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Disruptive Mood Dysregulation Disorder in Children with Autism Spectrum Disorder

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Abstract

Background

Irritability is one of the most important reasons for which children get referred to child mental health services. Disruptive mood dysregulation disorder (DMDD) is a diagnostic category characterized by severe and chronic irritability in children, and is associated with long-term adverse outcomes. However, little is known about DMDD in autism spectrum disorder (ASD). The aim of this study was to assess the prevalence of DMDD and the association between DMDD and comorbid psychiatric disorders in children with ASD.

Methods

Study participants consisted of 87 children with ASD aged 6-18 years, who were referred to a child psychiatry outpatient clinic at Osaka City University Hospital. A diagnosis of DMDD and associated symptoms were assessed through a semi-structured interview and the Child Behavior Checklist (CBCL).

Results

Of all study participants, approximately 17% (n=15) had a diagnosis of DMDD, although 60% (n=52) showed symptoms of DMDD. The total, internalizing and externalizing CBCL scores, as well as 6 of the 8 subscales (Anxious/Depressed, Social Problems, Thought Problems, Attention Problems, Delinquent Behavior, Aggressive Behavior), were significantly higher in children with DMDD than in children without DMDD.

Conclusions

Not assessing the frequency or duration of the symptomatic irritability is likely to increase the risk of over-diagnosing DMDD. Children with ASD and DMDD had more severe psychopathological symptoms than children with ASD without DMDD. Identifying DMDD in children with ASD may be helpful to the assessment of comorbid internalized/externalized symptoms as well as to the selection of appropriate therapeutic interventions, including pharmacotherapy.

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Key Words: Disruptive mood dysregulation disorder; Autism spectrum disorder; Depression; Anxiety disorder; Irritability

Introduction

Irritability is a common symptom in children and is one of the most common reasons for which children are referred to child and adolescent mental health services[1]. In a community sample, approximately 28%-51% of children aged 9-16 years experienced irritability-related symptoms[2]. Chronic and severe irritability is the cardinal symptom of Disruptive mood dysregulation disorder (DMDD), having newly appeared in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5)[3]. DMDD is associated with long-term poor and adverse outcomes[1].

DMDD is characterized by (a) severe recurrent temper outbursts that are grossly out of proportion in intensity or duration to the situation (on average three or more times a week), (b) persistent irritable/angry mood between temper outbursts throughout most of the day, nearly every day. In order to meet diagnostic criteria, these symptoms must be seen in at least two of three settings (at home, at school, with peers), and be present for at least 12 months. Additionally, DMDD cannot be first diagnosed prior to the age of 6-years-old or after the age of 18-years old, and should have an onset prior to the age of 10-years-old. Finally, DMDD cannot be diagnosed if the child has already been diagnosed with bipolar disorder (or any manic or hypomanic episode)[3].

In the 1990s, children with severe non-episodic, chronic irritability were considered to have pediatric bipolar disorder without significant manic episodes. However, some researchers were concerned about over-diagnosing children and using excessive medication to treat bipolar disorder. Longitudinal studies have suggested that such children showed a higher risk of having depression and anxiety in the future, rather than having bipolar disorder[4,5]. With respect to the prevalence of DMDD symptoms, which consist of temper outbursts and irritable mood, Dougherty et al report that 8% of 6-year-old children from a community sample have DMDD symptoms[6], while 26% of 6-12-year-old children from a clinical sample showed both symptoms for 6 months in at least 2 settings[7]. It must be noted that these reports used other assessment scales for psychiatric disorders for oppositional-defiant disorder (ODD), prior to the establishment of a DMDD diagnosis in the DSM-5 which could then frame the assessment of DMDD symptoms. Therefore, researchers have pointed out that these studies are limited in that they used arbitrarily chosen thresholds, without strictly applying the duration and frequency criteria of the symptoms as per the criteria set forth by the DSM-5 for the diagnosis of DMDD.

Irritability is also common in children with autism spectrum disorder (ASD), which is characterized by persistent deficits in social communication/interaction and restricted, repetitive patterns of behavior, interests, or activities, as described in the DSM-5[3]. Irritability presents as severe temper tantrums or over reactivity[8]. Maladaptive emotional responses in youth with ASD have a variety of phenotypes, including but not limited to irritability, poor anger control, temper tantrums, self-injurious behavior, and aggression[9,10]. These maladaptive emotional responses are directly associated with core features of ASD[11]. According to the DSM-5, children with ASD frequently present with temper outbursts only when, for example, their routines are disturbed. In such an example, the temper outbursts would be considered secondary to the ASD, and the child should not receive a diagnosis of DMDD[3]. However, with regards to whether children with ASD have comorbid DMDD or not, there are no studies strictly assessing or excluding the diagnosis of DMDD

which take into account the severity of the temper outbursts and irritable mood. The prevalence of DMDD in youth with ASD, and the association between a DMDD diagnosis and symptoms and other psychiatric comorbidities in youth with ASD, remain unknown. Therefore, the aims of this study are 1) to examine the prevalence of DMDD diagnoses and symptoms in children with ASD in a clinical sample, applying rigorous criteria based on the DSM-5, and 2) to examine the association between the diagnosis of DMDD and other psychiatric disorders (i.e. depression, anxiety) in children with ASD in a clinical sample.

Methods

Participants consisted of 94 children with ASD aged 6 to 18-years-old who had been referred to the child psychiatry outpatient unit in Osaka City University Hospital between April 2018 and December 2018. We excluded children with intellectual disability (n=5) who had difficulties in evaluating symptoms, as well as children with bipolar disorder (n=2), as assessed according to the DSM-5 diagnostic criteria. As a result, a total of 87 cases were retained for the study. We explained to participants and their parents the purpose of the study, as well as its procedures, potential risks, and alternatives to participation, and we obtained written informed consent from all children and their parents. The Human Subject Review Committee of Osaka City University reviewed and approved of the study protocol.

The diagnosis of ASD was based on the following sources: 1) a comprehensive developmental history from the parents, 2) an interview of both the child and their parents conducted by the clinician, 3) direct observations of the subject by the two child psychiatrists. Finally, a diagnosis of ASD was delivered according to the criteria of the DSM-5. To diagnose comorbid psychiatric disorders, we used the Japanese version of the Kiddie Schedule for Affective Disorder and Schizophrenia Present and Lifetime version (K-SADS-PL-J)[12]. This consists of a semi-structured interview designed to assess any current and past episodes of psychiatric disorders in children and adolescents according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text-revision (DSM-Ⅳ-TR) criteria and is administrated through interviews with the child and their parents. This diagnostic interview has good inter-rater reliability and concurrent validity[13]. After the diagnostic interview was completed, a multidisciplinary team meeting was held to decide on the most appropriate diagnosis for all participants.

Although ODD cannot co-exist with DMDD according to the DSM-5[3], because comorbidity of DMDD was of interest in this study, this exclusion was not applied here. Additionally, we collected information, from interviews, on 1) whether a child only had one parent (absence of father or mother), 2) family income, and 3) years of education of the parents. With regards to family income, we categorized households with public assistance or with an annual income of less than three million yen as “low-income”.

Assessment of DMDD diagnosis and DMDD symptoms

As previously mentioned, there are no diagnostic interview tools specifically designed for the diagnosis of DMDD that take into account the exact duration and frequency criteria in the DSM-5. Therefore, in this study, we created a new semi-structured interview, based on the DSM-5, to conduct with children’s parents. The content of the interview was based on the criteria of the DSM-5, and each item asked the following: 1) Does your child often have temper outbursts? How many times a week on average does your child have temper outbursts? When did the symptoms start? How long

does your child had the symptoms? 2) Does your child usually get irritable or angry? Does the irritable mood persist throughout most of the day? When did the symptoms start? How long has your child had the symptoms? 3) In how many situations are the symptoms present? Are the symptoms present at home, at school, with peers? On obtaining answers to these questions from the interviews with parents, we delivered a diagnosis of DMDD when 1) temper outbursts occurred 3 or more times per week and, at the same time, irritable mood lasted most of the day, 2) these symptoms had persisted for more than 12 months, 3) these symptoms were present in at least two of three settings (at home, at school, with peers), and 4) age at onset met the criteria set forth by the DSM-5. By assessing these symptoms, we investigated whether symptoms (temper outbursts and irritable mood) were of diagnostic severity or subthreshold (below the level warranted for a diagnosis of DMDD). For example, if the child had temper outbursts at least 3 times a week, we categorized these as "temper outbursts as symptoms of DMDD", and, if not, we categorized them as "subthreshold temper outbursts". Additionally, we examined the test-retest reliability and inter-rater reliability of this interview, re-obtaining participant answers again at a later date. The test-retest reliability was kappa=0.832 (n=23), with a 46-day interval on average, and the inter-rater reliability was 0.806 (n=13), with a 63-day interval on average. Both of the reliability rates were considered to confirm the validity of the interview.

Child Behavior Checklist (CBCL)

For the evaluation of holistic psychopathologies, we used the standardized Japanese version of Child Behavior Checklist (CBCL)[14]. CBCL is a parent-report rating scale of child psychopathology consisting of 113 questions developed by Achenbach and Dumenci[15]. Each question has the following response scale: 0=not true (as far as you know), 1=somewhat or sometimes true, 2=very often or often true. The scales consist of three domains (total score, internalizing score, externalizing score) and eight subscales (Withdrawal, Somatic Complaints, Anxious/Depressed, Social Problems, Thought Problems, Attention Problems, Delinquent Behavior, Aggressive Behavior).

Statistical Analysis

All statistical analysis was performed using SPSS version 25.0 statistical software (SPSS Japan, Inc., Tokyo, Japan). Descriptive data were presented as means, standard deviations (SD), medians, and ranges. A chi-square test or Fisher's exact test was used to compare categorical variables, as appropriate. A Mann-Whitney's U-test or Student's t-test was used to compare continuous valuables, whether the data was normally distributed or not. P-values$<$0.05 (using a two-sided probability) were considered to reflect statistical significance.

Results

Of all the participants (n=87), the mean age of the sample was 12.5-years-old (ranging from 6 to 17-years-old, SD 2.8), and 55.2% (n=48) of the sample was male. 21.8% (n=19) of the sample was from a low-income household, 25.3% (n=22) only had one parent (absence of father or mother). Parents' education had a mean duration of 13.9 years (ranging from 9-16 years, SD 1.6). The prevalence of comorbidities was 44.8% (n=39) for generalized anxiety disorder, 43.7% (n=38) for ODD, 39.1% (n=34) for attention-deficit hyperactivity disorder (ADHD), 32.2% (n=28) for social anxiety disorder, 19.5% (n=17) for major depressive disorder, 13.8% (n=12) for obsessive-compulsive disorder, 12.6% (n=11) for chronic tic disorder, 9.2% (n=8) for conduct disorder (CD), 8.0% (n=7) for adjustment disorder, 6.9% (n=6) for dysthymia, 6.9% (n=6) for Tourette disorder, 5.7% (n=5) for

Table 1. Prevalence of DMDD symptoms and diagnoses in children with ASD

	N=87	Symptoms present in at least 2 settings
Symptoms [(n (%)]		
temper outbursts	60 (69.0)	35 (40.2)
temper outbursts less than 3 times a week	25 (28.7)	
temper outbursts 3 or more times a week (DMDD symptoms)	35 (40.2)	
irritable mood	64 (73.6)	33 (37.9)
irritable mood present but less than most of the day	36 (41.4)	
irritable mood present most of the day (DMDD symptoms)	28 (32.2)	
temper outbursts and irritable mood	52 (59.8)	32 (36.8)
temper outbursts 3 or more times a week and irritable mood present throughout most of the day	23 (26.4)	16 (18.4)
DMDD diagnosis		15 (17.2)

DMDD, Disruptive Mood Dysregulation Disorder; and ASD, Autism Spectrum Disorder.

panic disorder, and 4.6% (n=4) for separate anxiety. Psychotropic agents had already been taken in 18.4% (n=16) of all children. Of these, 10 children had taken antipsychotics, 5 had taken stimulants, 1 had taken benzodiazepines. None of the children had taken antidepressants or a mood stabilizer.

Prevalence rate of DMDD diagnosis and DMDD symptoms

Table 1 shows the prevalence rates of DMDD-related symptoms by severity or by number of situations in which symptoms are present (≧2 or not), as well as the prevalence of DMDD diagnoses in the sample. Of the subjects, 69.0% (n=60) of children with ASD had temper outbursts, while 40.2% (n=35) of the sample showed temper outbursts as a DMDD symptoms (i.e. 3 or more times per week). Of all participants, 73.6% (n=64) of the children with ASD had irritable mood, but 32.2% (n=28) had irritable mood as a DMDD symptoms (i.e. for most of the day). With regards to both temper outbursts and irritable mood, 59.8% (n=52) had both symptoms at the same time, but 26.4% (n=23) had both DMDD symptoms (i.e. temper outbursts three or more times a week and irritable mood throughout for most of the day). Moreover, when considering the number of settings in which symptoms occur, the original 59.8% (n=52) of the children with both symptoms dropped to 36.8% (n=32) of the children with both symptoms present in at least 2 settings. Of the subjects, 26.4% (n=23) with both DMDD symptoms dropped to 18.4% (n=16) with both symptoms present in at least 2 settings. Consequently, 17.2% (n=15) of the subjects strictly met DMDD diagnostic criteria according to the DSM-5, incorporating frequency, duration, and the number of settings in which symptoms occur.

Sociodemographic factors and comorbidities

Table 2 shows the association between sociodemographic data, comorbidities, and DMDD. There were no significant differences between the DMDD and non-DMDD groups in terms of age, sex, family income (low income), or duration in years of parents' education. The rate of absence of a child's father or mother was significantly higher in the DMDD group than in the non-DMDD group [Odds ratio (OR) =6.81, 95% Confidence interval (CI) =2.06-22.49]. On investigating the association between comorbidities and a DMDD diagnosis, there were no significant differences in comorbid depressive or anxiety disorders between the DMDD and non-DMDD groups, while the DMDD group had a significantly higher comorbidity with ADHD (OR=4.00, 95% CI=1.23-13.02), and ODD/CD (OR

Table 2. DMDD and associated sociodemographic factors and comorbidities in children with ASD

	DMDD N=15	Non-DMDD N=72	U/t/χ^2	p	OR (95% CI)
Sociodemographic factors					
age [year: mean (SD)]	11.8 (2.6)	12.6 (2.8)	450.0[c]	0.312	
male [n (%)]	8 (53.3)	32 (44.4)	0.025[b]	0.876	1.09 (0.36-3.34)
Absence of parent [n (%)]	9 (60.0)	13 (18.1)	11.43[b]	0.001*	6.81 (2.06-22.49)
low-income [n (%)]	6 (40.0)	13 (18.1)	3.462[b]	0.063	3.03 (0.92-9.99)
parents education [year: mean (SD)]	14.0 (2.0)	13.8 (1.6)	357.0[c]	0.484	
IQ [score: mean (SD)]	102.6 (13.5)	93.6 (13.4)	1.882[a]	0.067	
Comorbidities					
Mood Disorders	7 (46.7)	20 (27.8)	2.046[b]	0.153	2.28 (0.73-7.10)
Anxiety Disorders	9 (60.0)	47 (68.1)	0.361[b]	0.558	0.70 (0.22-2.22)
ADHD	10 (66.7)	24 (33.3)	5.727[b]	0.021*	4.00 (1.23-13.02)
ODD/CD	14 (93.3)	24 (33.3)	17.96[b]	0.000*	28.0 (3.47-226)

[a]Student t-test; [b] Fisher's exact-test; [c]Mann-Whitney U-test; and * $p<0.05$.

Mood Disorders includes major depressive disorder, dysthymia, adjustment disorder. Anxiety disorders includes panic disorder, social anxiety disorder, separation anxiety, general anxiety disorder, obsessive compulsive disorder, tic disorder, Tourette's disorder. OR, Odds ratio; CI, Confidence interval. DMDD, Disruptive Mood Dysregulation Disorder; ADHD, Attention Deficit/Hyperactivity Disorder; ODD, Opposite Defiant Disorder; and CD, Conduct Disorder.

=28.00, 95% CI=3.47-226) than the non-DMDD group.

CBCL scores and DMDD diagnosis/symptoms

Table 3 shows CBCL scores (total, internalizing, externalizing, and the scores of the eight subscales) of the DMDD and non-DMDD groups. On comparing the two groups, the total scores, internalizing scores, and externalizing scores were significantly higher in the DMDD group than in the non-DMDD group. With regards to the CBCL subscales, 6 of the 8 subscale scores (Anxious/Depressed, Social Problems, Thought Problems, Attention Problems, Delinquent Behavior, Aggressive Behavior) were significantly higher in the DMDD group than in the non-DMDD group.

Discussion

Our results suggest two points: First, not assessing the frequency, duration and number of settings in which symptoms are present is likely to increase the risk of over-diagnosing children with ASD and DMDD. Applying strict criteria incorporating these considerations demonstrated that 17.2% of children with ASD in a clinical sample had a concurrent DMDD diagnosis according to DSM-5 criteria. Second, children with ASD and DMDD had a more severe and broader psychopathology than children with ASD without DMDD.

First, our findings suggest that DMDD is likely to become over-diagnosed in children with ASD. In our study, approximately 60% of the children with ASD had temper outbursts and irritable mood. However, the prevalence dropped to less than 50% when taking into consideration frequency criteria (temper outbursts 3 or more times a week and irritable mood throughout for most of the day) set forth by the DSM-5. Moreover, when taking into consideration the duration of the symptoms (symptoms

Table 3. The association of the CBCL scores and DMDD

	DMDD N=15	Non-DMDD N=72	U/t	p
CBCL, mean (SD)				
Total score	75.3 (11.2)	64.7 (8.66)	187.0[b]	0.002*
Internalizing score	75.3 (14.0)	65.4 (9.00)	2.45[a]	0.028*
Externalizing score	69.9 (9.83)	60.4 (11.4)	2.77[a]	0.007*
CBCL subscales				
Withdrawal	72.6 (11.4)	64.1 (8.39)	224.5[b]	0.09
Somatic Complaints	67.5 (11.7)	62.9 (10.4)	319.0[b]	0.183
Anxious/Depressed	74.3 (14.6)	62.8 (8.83)	216.5[b]	0.007*
Social Problems	69.0 (12.4)	61.5 (8.40)	262.5[b]	0.036*
Thought Problems	69.0 (14.0)	60.1 (11.3)	265.0[b]	0.034*
Attention Problems	71.5 (11.5)	61.8 (8.11)	3.63[a]	0.001*
Delinquent Behavior	67.3 (7.32)	59.0 (8.75)	214.0[b]	0.005*
Aggressive Behavior	68.9 (9.71)	60.6 (9.40)	220.0[b]	0.007*

[a]Student t-test; [b] Mann-Whitney U-test; and * $p<0.05$.
CBCL, the Children Behavior Checklist; and DMDD, Disruptive Mood Dysregulation Disorder.

present at least 12 months) and number of settings symptoms are present (at least 2 of 3 settings), the prevalence of rigorously defined DMDD dropped to 17.2% according to the criteria set forth by the DSM-5.

Previous reports have suggested that the prevalence of DMDD is wide-ranging. In a community sample, the 3-month prevalence of DMDD was 0.8%-3.3%[16], 5.3%[17], 8.2%[6], and 9.0%[18]. However, in a clinical sample, the prevalence of DMDD was higher than in the community sample. The 6-month prevalence of DMDD symptoms among 6 to 12-year-old children who had been referred to a child psychiatric outpatient clinic was 26%-31%[7,19]. However, these previous studies failed to use dedicated assessment measure of a DMDD diagnosis, and their diagnoses were performed by evaluating arbitrarily chosen criteria on the frequency or duration of symptoms, rather than the criteria set forth by the DSM-5. For example, most studies used alternative questionnaires or assessment tools for other psychiatric disorders for diagnosing DMDD prior to the development of the DSM-5. For this reason, previous reports often assessed the frequency or duration of DMDD symptoms as 'often or very often', and investigated the '3-month or 6-month' prevalence. Thus, these previous studies had investigated the prevalence of a form of 'proxy-DMDD', rather than true DMDD as defined by the DSM-5. Some researchers have expressed their concern about the validity of a DMDD diagnosis because of the high comorbidity of other psychiatric disorders in addition to its own high prevalence rate[20-22]. However, considering the likelihood of over-diagnosing DMDD in children with ASD as pointed out by our results, the prevalence of DMDD in previous studies may have been artificially inflated as a result of not strictly using criteria set forth by the DSM- 5.

Second, children with ASD and DMDD had significantly more severe psychopathological symptoms linked to depression and anxiety than those without DMDD. Several studies have noted the association between DMDD and other psychiatric disorders. In the 1990s to the mid-2000s, children with severe and chronic irritability had been diagnosed with pediatric bipolar disorder and

received treatment for bipolar disorder, for which there were growing concerns of overdiagnosis and overmedication. These concerns led to the establishment of newly defined criteria in the DSM-5 for the diagnosis of DMDD[3,23] alongside a number of epidemiological and prognostic studies on children with DMDD. As further evidence, a DMDD diagnosis in children means they are predisposed to higher future rates of depression and anxiety or a higher rate of comorbidity of depression and ODD, but not bipolar disorder[6,16]. Few reports had investigated DMDD in children with ASD. Axelson et al reported the prevalence of DMDD in a clinical sample consisting of OCD, CD, ADHD, depression, anxiety disorders, and autism, but the number of children with autism was too small to draw any conclusions about this subgroup[7]. Our study complements a previous study in which children with ASD comorbid with DMDD had more severe psychopathological symptoms characterized by depression and anxiety than children without DMDD.

In addition to symptoms of depression/anxiety, children with ASD and DMDD had a broader range of psychopathological symptoms. The significant prevalence of severe psychopathology linked to Delinquent Behaviors and Aggressive Behaviors from the CBCL subscales in the DMDD group may be explained by the evidence, as noted in previous studies, that DMDD itself often co-exists with ODD/CD characterized by behavioral problems[6,18,21,24]. The significant severe psychopathology linked to attention problems from the CBCL subscales in the DMDD group may also be explained by a previous suggestion that children with ADHD often have comorbid DMDD[25-27]. A previous study had demonstrated that ADHD, ODD, and CD were significantly more common comorbidities in the DMDD group than in the non-DMDD group in a general clinical sample. Our study has further demonstrated that ADHD, ODD, and CD are significantly more common comorbidities in patients with DMDD, even in an ASD clinical sample.

Irritability is a transdiagnostic factor which can be seen in various psychiatric diseases. Despite the difficulty in defining its characteristics, irritability tends to be a focus for treatment by psychotherapy and/or medication. Recent research has pointed to a link between irritability and emotional symptoms in late childhood/early adolescence[28]. Although Malhi et al suggested a preliminary model in which irritability was a symptom leading to the development of internalizing symptoms such as anxiety and depression[29], mechanisms of irritability remain unclear. As suggested in our study, DMDD co-exists with many other psychiatric disorders, specifically with ODD, and DMDD has been incorporated into a new subclassification of ODD in the International Classification of Diseases 11th Revision (ICD-11) as "ODD with chronic irritability/anger"[30]. As such, there remains a nosological debate to this day surrounding the conceptualization of irritability, and whether it is a developmental indicator of internalizing symptoms such as depression and/or anxiety, or a subordinate phenotype of externalizing symptoms such as ODD/CD. Our study clarifies that children with ASD and DMDD have higher scores on internalizing symptoms, such as depression/anxiety, and higher scores on externalizing symptoms, such as Delinquent Behaviors or Aggressive Behaviors, than children with ASD without DMDD. In this study, our results suggest that irritability itself may be an intermediate phenotype between internalizing and externalizing symptoms.

Clinical implications

There is no established management of therapeutic interventions for irritability in children, despite the need thereof in clinical settings. In children with disruptive behavior, research on psychosocial interventions has been limited, especially on parental management training and cognitive behavioral therapy, which have been suggested to be effective[31-33]. With regards to DMDD,

treatment options for children with DMDD are currently limited. A few studies have pointed to the efficacy of psychotherapy in children with DMDD[34,35], and in the case of children with DMDD comorbid with ADHD, a few reports have pointed to the efficacy of pharmacotherapy for the treatment of ADHD symptoms[36-39]. When treating irritability in child psychiatry, clinicians often face difficult decision on whether to treat the irritability directly, the comorbid condition, or both[1]. With regards to children with ASD, some antipsychotics have been approved to treat their irritability. However, due to the broad phenotype of irritability symptoms in ASD, there is no established treatment tailored to the severity and/or characteristics of the irritability. Therefore, treating irritability in children with ASD is often challenging for clinicians because of concerns surrounding the overassessment of symptoms and the overmedication with psychotropics. Although there is no evidence-based therapeutic intervention for DMDD children with ASD at this point, by extrapolation based on the treatment options in previous DMDD studies, our results may support the use of medication to treat severe irritability in children with ASD and DMDD.

Our study suggested that broad psychopathology, including symptoms of depression and anxiety, were more common in ASD children with DMDD than without DMDD. As mentioned above, although irritability is hard to recognize, recognizing DMDD in children with ASD may be helpful for identifying their internalizing and externalizing problems.

Strengths and limitations

A strength of our study was that it investigated the prevalence of DMDD in a clinical sample of children with ASD by performing a semi-structured interview tailored to DMDD. Additionally, though it was already known that DMDD was associated with depression and anxiety, our study enabled us to clarify that ASD children with DMDD had significantly more psychiatric problems, including symptoms of depression and anxiety, than children without ASD.

There were some limitations to our study. Firstly, in diagnosing DMDD, we used a parentreport assessment of DMDD symptoms. When assessing symptoms in children with ASD, a previous study had suggested that children with high functioning ASD (HFASD), who do not have intellectual disability, underreport their irritability symptoms[40]. In contrast, another study had suggested that both self-report and parent-report of irritability symptoms were reliable in male children with HFASD[41], revealing inconsistent findings. As such, in future studies, it may be useful to examine both self-reports and parent-reports. Secondly, irritability symptoms may have been dampened or hidden entirely since 10 children were already taking antipsychotics. However, 1 of 10 children taking antipsychotics also met diagnostic DMDD criteria as set forth in the DSM-5, and the other 9 children did not meet diagnostic DMDD criteria from before the initiation of their antipsychotics treatment to the time of symptom evaluation. Therefore, any effects on the results were considered small. Finally, this study was based on a clinical sample of children with ASD from a single institution, thereby warranting careful interpretation in the generalization of our results to all children with ASD.

Conclusion

In conclusion, the prevalence of children with ASD and DMDD was as high as approximately 17%, and they may have been likely to be over-estimated. ASD children with DMDD are more likely to have broad psychiatric problems, including depression and anxiety at a symptomatic level. Identifying DMDD in children with ASD may be helpful for the risk management of exacerbating symptoms of depression or anxiety, both at the time of assessment and in the future, and for the

development of appropriate therapeutic interventions. Since this is a cross-sectional study, further longitudinal studies are needed to both investigate in further depth the clinical course of children with ASD and to contribute to their appropriate treatment and intervention.

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Can a General-purpose Interactive Robot Detect Poor Cognitive Function? A Pilot Study

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Abstract

Background

Neuropsychological examinations have been routinely used to screen for dementia. However, these require human resources, and the subject might feel psychologically burdened by the human examiner. We investigated whether a robot could be used to screen for dementia.

Methods

We used a general-purpose humanoid interactive robot to conduct the Hasegawa Dementia Scale Revised (HDS-R), modified for the robot (robot test). We recruited 12 patients with mild to moderate Alzheimer's disease (AD) and 4 patients with mild cognitive impairment (MCI) from the outpatient department of Osaka City Kosaiin Hospital. We recruited 10 healthy controls (HC) from patients' spouses. The subjects took the robot test, the Mini Mental State Examination (MMSE), and HDS-R on the same day. The scores for the robot test (robot scores) were calculated by a human. To demonstrate correlations between scores, we used the Spearman's rank-correlation method. Between-group comparisons of scores were assessed using the nonparametric Kruskal-Wallis test, with multiple comparison corrections performed using the Steel-Dwass procedure.

Results

There were no dropouts in the robot test. The robot scores correlated significantly with the scores of the MMSE (rho=0.814, $p<0.001$) and HDS-R (rho=0.855, $p<0.001$). Moreover, robot scores in the AD group were significantly lower than in the MCI ($H=2.93$, $p<0.001$) and HC ($H=1.28$, $p=0.009$) groups.

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Conclusions

Although the interviewer is a general-purpose interactive robot, it is able to talk and get the necessary information to detect poor cognitive function in elderly participants.

Key Words: Interactive robot; Alzheimer's disease; Screening; Neuropsychological examination

Introduction

Early detection of dementia is important because it increases the potential for an effective intervention. For example, interventions such as drug therapy are most effective when they are started early[1]. Brodaty et al reported that neuropsychological examinations such as General Practitioner Assessment of Cognition, Mini-Cog, and Memory Impairment Screen were suitable for dementia screening in general practice[2]. However, since these need a human examiner and have labor-associated costs, it is sometimes difficult to screen dementia due to lack of human resources. Furthermore, the elderly people who undergo cognitive function examinations may feel psychologically burdened by human examiners. Kobayashi et al showed that, due to psychological burden, elderly people may not perform to their full ability in examinations conducted by a human compared to examinations performed using a personal computer[3]. Therefore, automatic and inexpensive tests that do not require a human examiner at the time of testing are needed to screen for dementia.

Previous studies of automated dementia screening have mainly focused on developing screening software for personal computers or tablet devices. However, as pointed out by Kobayashi, the use of a mouse is often difficult for the elderly[3], and examinations using a touch panel is currently preferred. Tsuji et al reported a computer-based test that conducts a neuropsychological examination for elderly subjects with dementia using a touch panel[4]. Onoda and Yamaguchi developed the revision of Cognitive Assessment for Dementia, iPad version (CADi2) and used it for primary mass screening in community-based medical facilities[5].

Recent advances in robot technology also have the potential to enable automated neuropsychological examinations. Several studies have demonstrated the usefulness of robot therapy to treat the behavioral and psychological symptoms of dementia. Gustafsson et al reported that their cat robot increased well-being and quality of life for some individuals with dementia[6]. Treatment with PARO (Daiwa House Industry, Osaka, Japan) a baby seal-like robotic pet was reported to be effective for stress reduction[7] and resulted in reductions in the use of psychoactive medications in elderly people with dementia[8]. In the MARIO Project, it has been reported that the companion robot MARIO may be a useful tool in mitigating depression and loneliness for people with dementia[9]. It is currently unknown whether touch panel devices or conversational robots are more effective for neuropsychological examinations. However, considering robots have been used for elderly patients with dementia as mentioned above, robots likely have the potential to greater reduce the psychological burden than touch panel devices.

We hypothesized that a general-purpose interactive robot would be helpful to assess cognitive function because of the possibility of reducing medical expenses and psychological burden in patients. Hence, we have developed a neuropsychological examination auto-interviewing robot using a general-purpose interactive robot.

In this study, we present our neuropsychological examination auto-interviewing robot and

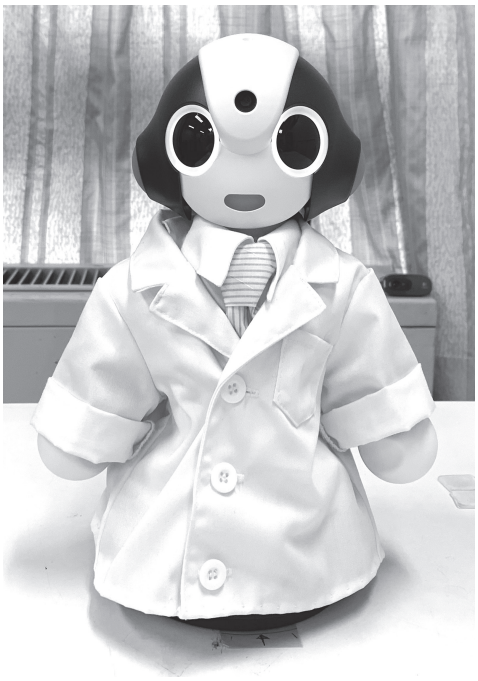

Figure 1. Image of SOTA with white coat.

investigate whether the robot can communicate with and get the necessary information to detect poor cognitive functioning from healthy and cognitive impaired elderly participants.

Methods

Robot architecture

In this study, we used a general-purpose humanoid interactive robot, SOTA (Vstone Co. Ltd., Osaka, Japan), as shown in Figure 1. SOTA has been previously used in a study investigating the use of robots for recreational activities in nursing homes[10]. SOTA measures 280 mm in height and weighs 800g. We used the NTT Data Cloud Robotics Platform to implement SOTA's communication and testing program.

The main function of SOTA was to record the participant's voice and synthesize speech. SOTA communicated with a participant via a loop incorporating the following steps: (a) participant speaks to SOTA; (b) SOTA records the participant's voice with its microphone; (c) voice data is transferred to the NTT Data Cloud Robotics Platform; (d) in the cloud platform, voice data is converted to text data; (e) a response to the text data is generated according to the scenario; (f) an audible response is synthesized; (g) the synthesized audible response is transferred to SOTA; and (h) SOTA responds with a synthesized voice.

Particularly, in step (e), when SOTA received an unexpected response (or no response), SOTA was designed to nod in response and continue to the next question. When the correct reply was received, SOTA repeated the answer.

Robot test

The experiment was conducted in Osaka City Kosaiin Hospital after a baseline examination including a cognitive function test. If for any reason it was not able to be conducted on the same day as the baseline examination, the experiment was conducted as quickly as possible (i.e. within a

Table 1. The robot's brief script and instructions for administration of the test

	Score	Script (originally in Japanese)	Instructions for administration
		I' m SOTA.	Introduction for test.
Q1	1	Tell me your birthday.	
Q2	1	How old are you?	Within 1 year of the patient's correct age
Q3	3	Remember three objects. Cherry, Cat, Train.	Then asks the patient for all three after the robot has said them. Give a point for each correct answer.
Q4	2	Remember three or four numbers, and say them in reverse order.	If the participant answered the three numbers correctly, then proceed to four numbers.
Q5	2	Serial sevens (starting from 90).	83, 76 (One point for each correct)
Q6	6	Recall the 3 objects repeated above.	Give 2 points for each correct. If a patient could not answer completely, give hints and ask one more time. Give 1 point for each correct with a hint.
Q7	5	Remember the following short story: "Yesterday I sent a flower to the teacher who had a reunion in Kyobashi, Osaka."	Give 1 point for each correct word (total five words in Japanese) and subtract 5. In case of a negative score, it is assumed to be 0 points.
Q8	3	Look for similarity between; "an orange and apple", "a bicycle and bus", "a drum and whistle".	Give 1 point for each correct word. "Fruit" "Vehicle" "Musical instrument"
Q9	3	What is the date/month/year?	One point for each correct
Q10	1	Where are we?	"Kosaiin" or "Hospital"
Q11	5	Recall the previous short story.	Give 1 point for each correct word and subtract 5. In case of a negative score, it is assumed to be 0 points.
Q12	1	Say my name.	"SOTA"

month), to avoid any changes to the participant's cognitive abilities between experiments. Participants were guided to the room and introduced to SOTA. We asked the participant to follow any instructions given by SOTA but did not give any advice such as "how to use a robot" during the test.

We created a scenario in which a cognitive function test, with a duration of 10 minutes, was conducted by SOTA (Table 1) in Japanese. The test scenario was developed with reference to the Hasegawa Dementia Scale Revised (HDS-R), which is a validated screening test for dementia[11], and is widely used in Japan. Because of restricted nature of robot conversation, we modified the HDS-R to be suitable for a robot. In particular, recalling 5 objects and generating vegetables were removed. Instead of them, Q7 (immediate recall of short story), Q8 (conceptualization), and Q11 (delayed recall of short story) were added. Furthermore, to get used to the dialogue with the robot, Q1 (birthday) was added as the first question, which is relatively easy to answer even for participants with dementia. Q12 (recall robot's name) was added to verify whether cognitive function can be tested in a natural conversation. To minimize learning effects, we modified questions relating to delayed recall and changed the starting number for the serial sevens so that it differed from the original HDS-R.

After the robot test, a human graded the recorded interview according to a manual (Table 1). The score distribution was determined with reference to HDS-R.

Participants

A total of 26 participants enrolled in the study and completed a baseline examination, including the Mini-Mental State Examination (MMSE) and the HDS-R conducted by a clinical psychologist.

Participants were either outpatients at Osaka City Kosaiin Hospital, Japan, from April 2017 to December 2017, or patients' spouses. Participants were assigned to one of three groups: mild to moderate Alzheimer's disease (AD), mild cognitive impairment (MCI), or healthy controls (HC).

The AD group met the following inclusion criteria: (a) met the National Institute of Neurologic, Communicative Disorders and Stroke, AD and Related Disorders Association, Alzheimer's criteria for probable AD[12]; and (b) scored 11 or more points on the MMSE[13]. MCI patients were defined as having complaints about cognitive impairment, and observable cognitive decline, but whose basic daily living functions were normal. They met the revised MCI criteria[14]. The HC group met the following inclusion criteria: (a) had never been diagnosed with dementia at any hospital; (b) were able to live independently; and (c) had no complaints of memory loss.

We obtained written informed consent from all participants. The study protocol was approved by the Ethics Committee of Osaka City Kosaiin Hospital in accordance with the declaration of Helsinki.

Statistical analysis

Analyses of the demographic and clinical characteristics were performed with Easy R (EZR) (Saitama Medical Center, Jichi Medical University, Saitama, Japan)[15]. EZR is a graphical user interface implemented in R 2.13.0 (R Foundation for Statistical Computing, Vienna, Austria). Between-group comparisons of MMSE, HDS-R and age were assessed by using the nonparametric Kruskal-Wallis test, with multiple comparison corrections performed using the Steel-Dwass procedure. Categorical variables such as sex were compared with Fisher's exact tests. To demonstrate correlations between test scores produced by the robot and humans, we used the Spearman's rank-correlation method. Alpha values less than 0.05 were considered significant.

Results

Acceptance of the robot

No participants dropped out of the robot tests. The participants did not get angry with or confused by our robot enough to prevent the continuation of the robot test.

Demographic characteristics & baseline examinations

For the AD, MCI, and HC groups, sex ratios (female/male) were 4/8, 0/4, and 9/1; the median [first quartile point (Q1), third quartile point (Q3)] ages were 79.00 [74.25, 84.25], 75.50 [73.00, 78.50] and 73.50 [70.25, 75.00] years old; the median MMSE points [Q1, Q3] were 21.50 [20.75, 22.00], 25.00 [25.00, 25.25] and 26.50 [24.50, 27.75]; the median HDS-R points [Q1, Q3] were 18.00 [14.00, 19.00], 23.00 [19.50, 26.25] and 29.00 [28.25, 30.00].

There was a significant group difference of sex ratio among the AD, MCI, HC groups ($p=0.002$, Fisher's exact tests). There were fewer male participants in the HC group compared to AD and MCI group.

The AD group were significantly older than HC group ($H=2.40$, $p=0.044$). The median age of the MCI group was not significantly different compared to the AD ($H=0.86$, $p=0.668$) and HC ($H=1.28$, $p=0.403$) group.

The AD group had significantly lower MMSE scores than both the MCI group ($H=2.78$, $p=0.015$) and HC group ($H=3.21$, $p=0.004$). There was no significant MMSE score difference between the MCI and HC groups ($H=1.00$, $p=0.576$).

The AD group had significantly lower HDS-R scores than the HC group ($H=3.98$, $p<0.001$). MCI group tended to have lower HDS-R scores than HC group ($H=2.30$, $p=0.056$).

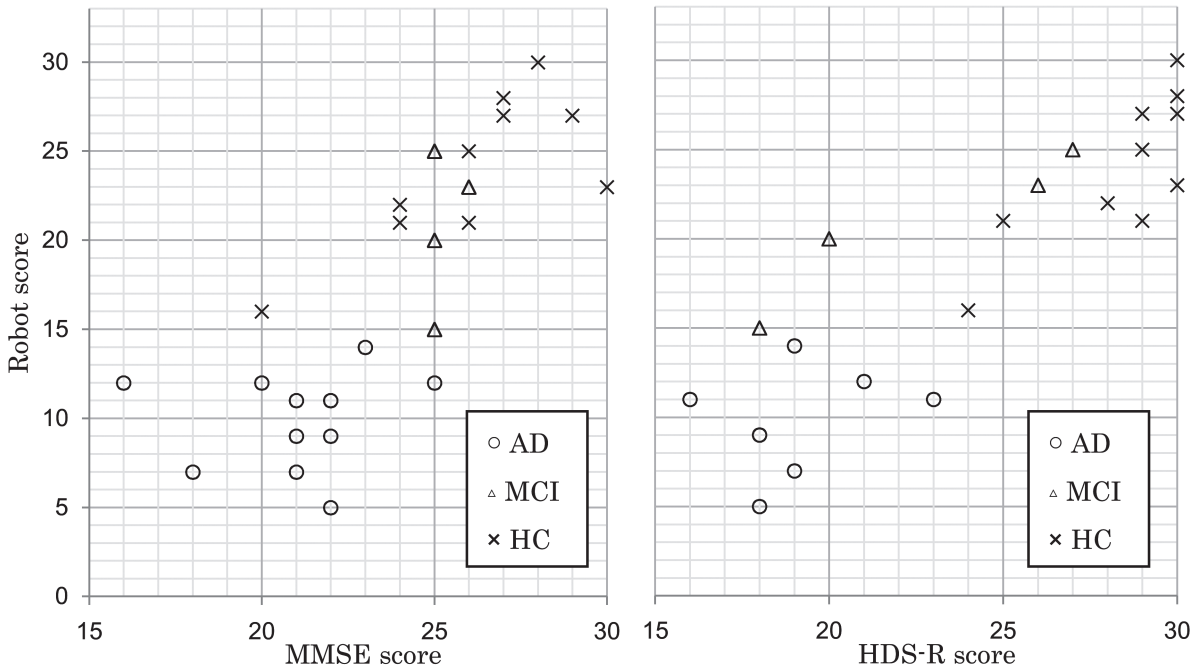

Figure 2. Score correlation between robot scores and neuropsychological examinations. Abbreviations: AD, Alzheimer's disease; MCI, mild cognitive impairment; HC, healthy control; MMSE, Mini-Mental Scale Examination; and HDS-R, Hasegawa Dementia Scale Revised.

Table 2. Average scores of each question of robot test

Question (max point)	Average score±SD			p value
	AD	MCI	HC	
Q1. Birthday (1)	1.00±0.00	1.00±0.00	1.00±0.00	NaN
Q2. Age (1)	0.83±0.39	1.00±0.00	1.00±0.00	0.308
Q3. Repeating 3 words (3)	2.33±0.78	2.75±0.50	2.40±0.84	0.649
Q4. Digits backward (2)	0.92±0.79	1.25±0.96	1.30±0.67	0.488
Q5. Calculation (2)	1.42±0.67	2.00±0.00	1.50±0.71	0.298
Q6. Recalling 3 words (6)	0.25±0.62	3.00±2.58	5.30±1.06	<0.001
Q7. Immediate recall of short story (5)	0.08±0.29	3.00±1.41	2.80±1.40	<0.001
Q8. Conceptualization (3)	2.00±1.04	2.25±0.96	2.90±0.32	0.055
Q9. Orientation to time (3)	0.67±0.98	2.00±0.00	3.00±0.00	<0.001
Q10. Orientation to place (1)	0.50±0.52	0.75±0.50	1.00±0.00	0.028
Q11. Delayed recall of short story (5)	0.00±0.00	1.75±1.71	1.70±1.95	0.015
Q12. Recall robot's name (1)	0.00±0.00	0.00±0.00	0.10±0.32	0.467
Total (33)	10.00±2.63	20.75±4.35	24.00±4.19	<0.001

P values represent group differences among AD, MCI, and HC groups with the Kruskal-Wallis test. Abbreviations: AD, Alzheimer's disease; HC, healthy control; HDS-R; Hasegawa Dementia Scale Revised; MCI, mild cognitive impairment; MMSE, Mini-Mental Scale Examination; NaN, not a number; and SD, standard deviation.

Robot scores

Figure 2 shows score correlations between the robot test and the neuropsychological examinations MMSE and HDS-R. There was a significant correlation between the robot scores with the MMSE (rho

=0.814, p<0.001) and the HDS-R scores (rho=0.855, p<0.001).

Robot scores in the AD group (median, 11.0) were significantly lower than those in the MCI group (median, 21.5; H=2.93, p<0.001) and HC group (median, 24.0; H=3.97, p=0.009). There was no significant difference in robot scores between the MCI and HC groups (H=1.28, p=0.407).

Table 2 shows the average scores of each question of the robot test. There were significant group differences in Q6 (recalling 3 words), Q7 (immediate recall of short story), Q9 (orientation to time), Q10 (orientation to place) and Q11 (delayed recall of short story). All participants in the 3 groups answered Q1 (birthday) correctly. Only HC participants answered Q12 correctly.

Discussion

We performed a pilot study for the use of a general-purpose interactive robot to screen for dementia. The robot conducted a modified HDS-R, which was completed by all participants. There were significant correlations between the robot scores and MMSE and HDS-R scores conducted by a human psychologist. Previous studies have supported the usefulness of the MMSE and HDS-R as screening tests for Alzheimer's disease[11,16]. Moreover, robot scores of 14 or less were obtained only in patients with dementia and not in those with MCI or HC. These results suggest our robot scores are useful to detect poor cognitive functioning in healthy and cognitive impaired elderly participants. Therefore, our novel robot was able to talk to and get the necessary information from elderly patients to make such a detection.

It is worth noting that there were no dropouts in the robot test despite some of the participants included having mild to moderate AD. This supports the idea that patients with mild to moderate AD can accept a general-purpose interactive humanoid robot in well-structured interactions as an interviewer. Furthermore, although the robot represents an inspector, it appears that there was no psychological burden that would make psychological examination difficult to complete in this study. However, because our study focused on screening and was not targeted at patients with severe dementia, it is still unclear whether a patient with severe dementia could communicate with our robot. A previous study has shown that a humanoid robot can be used with institutionalized patients with advanced dementia, but in that study, unlike here, the robot was remotely operated[17].

In the robot test, the breakdown of the subject's score was comparable to that of the conventional test. The loss of recent memory (Q6, recalling 3 words; Q11, delayed recall of short story) and orientation (Q9, orientation to time; Q10, orientation to place) was striking while short-term memory loss (Q3 repeating 3 words; Q4, digits backward) was relatively preserved in AD and MCI patients. This preservation of short-term memory is in line with previous studies showing that short-time memory is intact in patients with a damaged medial temporal lobe, such as AD patients[18,19].

There are three important tasks revealed by this study regarding our modified HDS-R, and it will be necessary to improve the content of the questions for future research. First, the administration time may be long. In this study, we tested various types of questions to investigate what kind of question is best suited for a robot. Therefore, the robot test can be shortened in the future. Second, internal consistency could be improved. Some questions (Q1-5, Q12) were either too easy or too difficult to distinguish AD or MCI participants from HC. Third, participants in the MCI and HC groups could not be clearly differentiated by our robot test. The cause of this could be the small sample size of the experiment, or the difficulty of the robot test. The difficulty of the robot test was designed using HDS-R as a reference, which is designed to screen for dementia, not MCI. Therefore,

the robot test was considered to be too easy to distinguish MCI from HC.

Compared to the Montreal Cognitive Assessment (MoCA), which has been reported as a useful screening tool for MCI[20], our test lacks a trail making test because our robot can only interact verbally in this study. When MMSE and a trail making test were combined, the accuracy and precision of mild dementia screening was reported to improve[21]. Similarly, to accurately screen for MCI we might need to include a trail making test in future studies. Some commercially available robots such as PEPPER (Soft Bank Corp., Tokyo, Japan) have touch panels to aid in communication, and therefore could easily incorporate a trail making test into our test.

There are three advantages to our robot test compared to the paper based conventional test. First, no expert is required to conduct the cognitive function tests. Second, we can standardize the method of conducting cognitive function tests. Third, since the recorded interviews are scored, labor-associated costs are minimized. Bearing in mind privacy issues, recorded interviews can be sent electronically and scored anonymously at a centralized location. Considering that SOTA has been studied for use as a recreational robot in nursing homes, we believe that our robot is better suited to support dementia screening in nursing homes that lack the necessary human resources.

This study has several limitations that should be considered when interpreting the data. First, the number of participants was small. There was no precedent for the application of an interactive robot to a neuropsychological examination. Therefore, we considered that the number of cases was appropriate as an initial pilot study aimed at optimizing the protocol for future studies. Second, the sex ratio and age of participants was biased, and it is possible that sex and age may influence scores in the robot test. However, strong correlations between robot scores and the MMSE (or HDS-R) suggests that the robot scores are not affected by the sex and age of the examinee. Third, responses to the robot were not quantified, therefore we could not demonstrate a statistical association between the severity of dementia and the responses to the robot. Finally, there is a possibility that the learning effect occurred, because MMSE and HDS-R were performed before the robot test. It is possible that the task was performed appropriately as a result of having experienced the MMSE and HDS-R, even if the instruction by the robot was inadequate. However, most of the instructions in the robot test were modified for the robot conversation from original HDS-R. Furthermore, to minimize learning effects, we modified questions relating to delayed recall and changed the starting number for the serial sevens. Therefore, we assume the learning effect did not significantly affect the robot score or the interactions between participants and robot in this study.

Conclusions

Even though the interviewer is a general-purpose interactive robot, our novel robot was able to talk to and get the necessary information from elderly participants to detect poor cognitive functioning. Our pilot study suggests that a general-purpose interactive robot could be a promising support tool for dementia screening. Although our robot currently requires human scoring, it can still reduce human cost because a non-specialized human can effectively score recorded interviews from robot tests in their spare time. We expect that in the future, interactive robot tests will become a valid and reliable tool for clinicians when screening for dementia in nursing homes that lack appropriate human resources.

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Efficacy of Practical Training Using a Simulator for Auscultation of Lung Sounds

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Abstract

Background

Auscultation training using a simulator before professors' rounds has been performed in fifth-year medical students since 2012. The objective of the present study was to assess whether students could differentiate abnormal lung sounds in patients and whether their performance improved during professors' rounds after simulation-based training.

Methods

Fifth-year medical students were divided into a simulation-based training group (Group S) and a non-simulation training group (Group N). In Group S, auscultation training using a simulator was performed just before professors' rounds. In Group N, students listened to recordings of four abnormal lung sounds. The students auscultated lung sounds in patients and mentioned the identified lung sounds. Teachers assessed the students' attitudes and auscultation skills.

Results

There were nine students in Group S and nine in Group N. The accurate response rate for "no rales" was significantly higher in Group S than in Group N ($p=0.003$). With regard to fine crackles and coarse crackles, the accurate response rates tended to be higher in Group S than in Group N ($p=0.056$ and $p=0.053$, respectively). Standard precautions, communication, and enthusiasm as students' attitudes showed no significant differences between Group S and Group N. On the other hand, auscultation skills were significantly better in Group S than in Group N ($p<0.05$).

Conclusions

Auscultation training using a simulator helped medical students differentiate abnormal lung sounds in patients. This training also improved auscultation skills but did not improve the attitudes of medical students during professors' rounds.

Key Words: Auscultation; Simulation-based education; Lung sounds

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Introduction

Chest auscultation is an important, simple, and non-invasive skill among medical workers, which provides clinical information about lung structure and function. Therefore, medical students should be able to auscultate patients accurately before graduation.

Simulation-based education has recently been adopted worldwide, as well as in Japan[1-3]. Miller presented the assessment of clinical skills as a pyramid with the following four levels: knows, knows how, shows how, and does[4]. Simulation is a 'shows how' level and is before the 'does' level, which is performed before clinical practice. The efficacy of the lung sound simulator Mr. Lung® has been reported, and it has been assessed whether medical students could differentiate abnormal lung sounds from the simulator[5,6]. However, there are few reports on whether auscultation training is practically effective for differentiating abnormal lung sounds in patients.

Auscultation training using a simulator before professors' rounds has been performed in fifth-year medical students since 2012 at Osaka City University[7]. We previously reported that self-assessment of auscultation with regard to abnormal lung sounds after auscultation training using a simulator improved the confidence of students to differentiate lung sounds when compared with the findings before simulation training. However, our previous report did not clarify whether the students could differentiate abnormal lung sounds in real patients.

The objective of this study was to assess whether students could differentiate abnormal lung sounds in patients and whether their performance improved during professors' rounds after simulation-based training. We hypothesize that auscultation training using a simulator helps medical students differentiate abnormal lung sounds in patients, and also improves the auscultation skills or attitudes of medical students during professors' rounds.

Methods

Clinical clerkship of fifth-year students in Osaka City University involves division of students into groups (four or five students) and rotation around 18 departments of Osaka City University Hospital for 2 weeks each. The present study was performed between November 2017 and February 2018, and it enrolled four student groups. The participants were fifth-year medical students who provided consent for study inclusion. They were divided into a simulation-based training group (Group S) and a non-simulation training group (Group N). The four student groups were alternately included in these two training groups.

In Group S, auscultation training was performed using a simulator for 1 hour just before professors' rounds, and it was attended by students, doctors, and nurses. The Mr. Lung® (Kyoto Kagaku, Kyoto, Japan) simulator was used. Four abnormal sounds, including fine crackles, coarse crackles, wheezes, and rhonchi, were auscultated in the simulator using a stethoscope, with explanations from teachers who were respiratory specialists. During simulation training, the teachers also provided information about standard precautions, communication, and favorable attitudes for professors' rounds. In Group N, students listened to recordings of the four abnormal lung sounds and received explanations from the same teachers, who provided explanations to Group S, for 1 hour just before professors' rounds. In this group, the teachers also provided information about standard precautions, communication, and favorable attitudes for professors' rounds.

During professors' rounds, all participants auscultated lung sounds in patients who agreed to this study, and they mentioned the identified lung sounds in assessment sheets (Fig. 1). Additionally, the

Assessment sheet

	Fine crackles	Coarse crackles	Wheezes	Rhonchi	No rales	N/A
Patient①						
Patient②						
Patient③						
Patient④						
Patient⑤						
Patient⑥						

Standard precaution hand sanitizer, stethoscope				Communication approaching patients				Enthusiasm attitude in professors' round				Auscultation skill spot, length			
good	not good	not bad	bad	good	not good	not bad	bad	good	not good	not bad	bad	good	not good	not bad	bad

Figure 1. Assessment sheet. Students mentioned the lung sounds on the top, and teachers mentioned the attitudes and auscultation skills of the students at the bottom of the sheet.

teachers mentioned the attitudes of the students during professors' rounds and their auscultation skills in the same assessment sheets.

The study protocol was approved by the appropriate Institutional Ethics Committee (Osaka City University, Graduate School of Medicine; approval no.: 2865).

Statistical analysis

Statistical analyses were performed with JMP (version 10; SAS Institute, Inc., Cary, NC, USA). Non-parametric analysis was performed for comparison of the two groups. The Mann-Whitney *U* test was used to compare abnormal lung sounds, students' attitudes during professors' rounds, and students' auscultation skills. A p-value <0.05 was considered significant.

Results

In this study, nine students were included in Group S and nine were included in Group N. In Group S, four students auscultated two patients and five students auscultated four patients. In Group N, eight students auscultated three patients and one student auscultated four patients.

Differentiation of abnormal lung sounds was better in Group S than in Group N

The results of accurate responses for lung sounds in Group S and Group N are presented in Figure 2. Both groups did not listen to wheezes and rhonchi, and thus, we presented graphs of fine crackles, coarse crackles, and no rales (normal lung sounds). The accurate response rate for 'no rales' was significantly higher in Group S than in Group N ($p=0.003$). With regard to fine crackles and coarse crackles, the accurate response rates tended to be higher in Group S than in Group N ($p=0.056$ and

	Fine crackles	Coarse crackles	Wheezes	Rhonchi	No rales
Group S cumulative total number, correct answers(%)	9, 8(89%)	10, 5(50%)	0	0	9, 6(67%)
Group N cumulative total number, correct answers(%)	14, 7(50%)	5, 0(0%)	0	0	9, 0(0%)

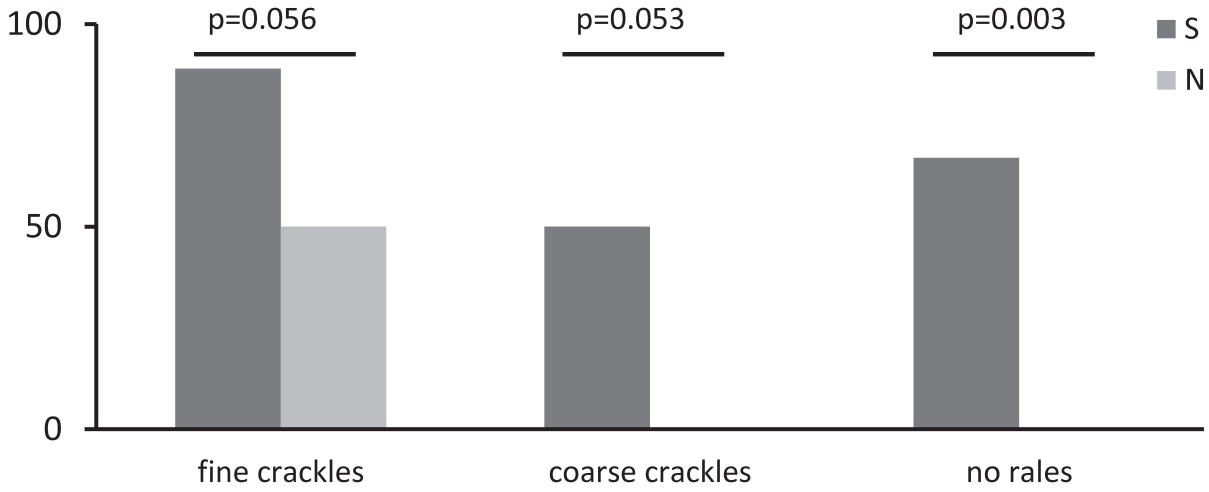

Figure 2. Results of lung sounds in Group S and Group N. Group S is a simulation-based training group and Group N is a non-simulation training group. Both groups did not listen to wheezes and rhonchi. The accurate response rate for 'no rales' is significantly higher in Group S than in Group N (graphs on the right). With regard to fine crackles and coarse crackles, the accurate response rates tend to be higher in Group S than in Group N (graphs on the left and in the middle, respectively).

p=0.053, respectively).

Simulation-based training improved students' auscultation skills but not their attitudes during professors' rounds

Students' attitudes during professors' rounds are presented in Figure 3, and their auscultation skills during professors' rounds are presented in Figure 4. Standard precautions, communication, and enthusiasm with regard to students' attitudes were not significantly different between Group S and Group N. On the other hand, auscultation skills were significantly better in Group S than in Group N ($p<0.05$). As of auscultation skills, eight students were 'good' and one student was 'not good' in Group S, while five students were 'good' and four students were 'not good' in Group N.

Discussion

The findings of the present study indicate that auscultation training for lung sounds using a simulator might help students accurately differentiate abnormal lung sounds. Arimura et al reported the efficacy of auscultation training for lung sounds using a simulator among medical students[6]. They assessed whether students could differentiate four abnormal lung sounds in a lung sound simulator and not in patients. Our study assessed students' auscultation skills in patients; however,

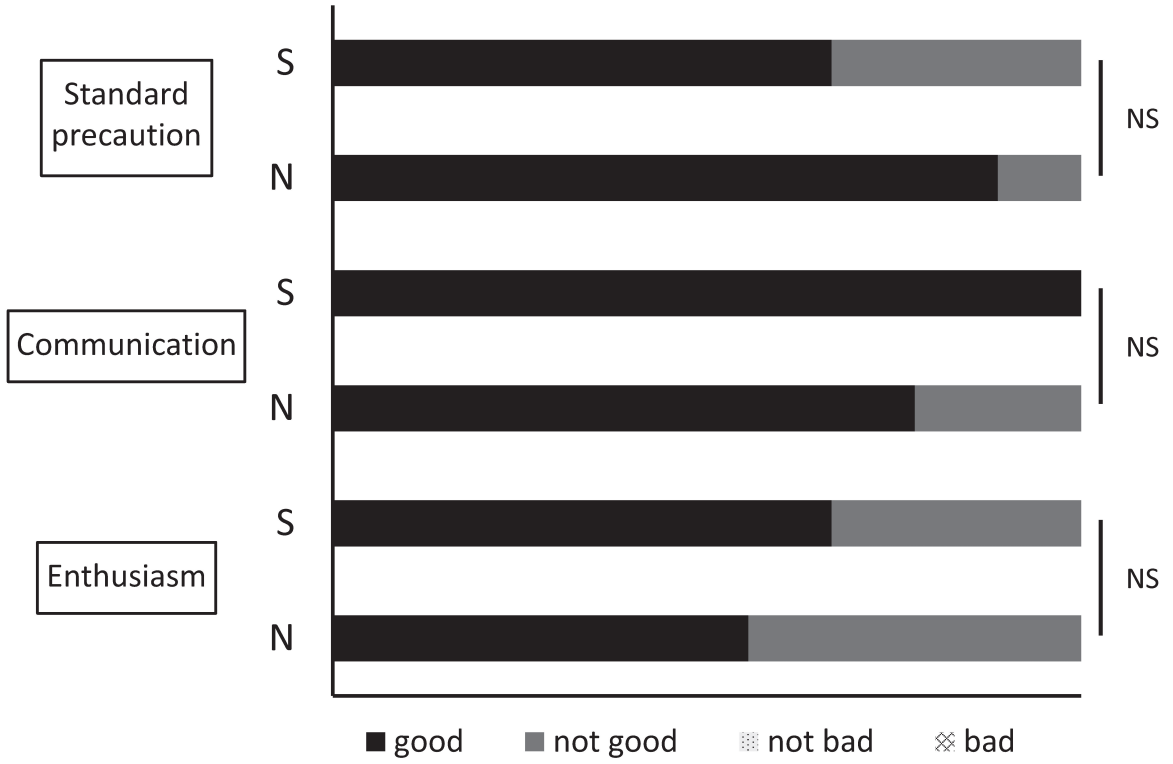

Figure 3. Results of students' attitudes during professors' rounds in Group S and Group N. Group S is a simulation-based training group and Group N is a non-simulation training group. There are no significant differences between the two groups.

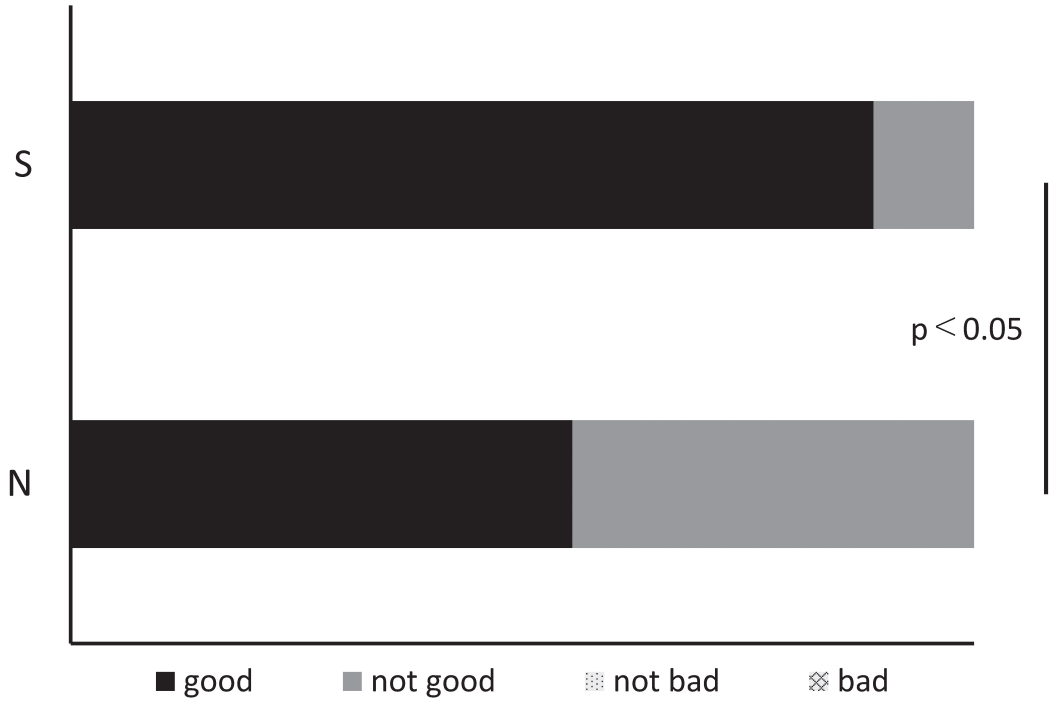

Figure 4. Results of students' auscultation skills during professors' rounds in Group S and Group N. Group S is a simulation-based training group and Group N is a non-simulation training group. The auscultation skills are significantly better in Group S than in Group N. Eight students were 'good' and one student was 'not good' in Group S, while five students were 'good' and four students were 'not good' in Group N.

only two abnormal lung sounds (fine crackles and coarse crackles) and normal lung sounds (no rales) were evaluated. Although further research involving other abnormal lung sounds is needed, the findings of our study indicate that simulation-based training might improve the ability of students to auscultate lung sounds in the clinical setting.

Although simulation-based training improved auscultation skills, it did not improve the attitudes of medical students during professors' rounds. In auscultation training using a simulator, students auscultated sounds from the simulator with a stethoscope. The use of a stethoscope might have helped improve their auscultation skills. Mangione et al reported that patient revisits were important for medical students and residents to improve their auscultation skills[8]. Therefore, in the present study, simulation-based training might have improved the auscultation skills of the students in Group S. On the other hand, simulation-based training did not improve their attitudes, including standard precautions, communication, and enthusiasm. Abe et al recently reported about the educational benefits associated with the use of a robotic patient simulation system for the development of clinical attitudes[9]. The robotic patient was similar to a real patient, which might have helped improve students' attitudes. To improve students' attitudes with our simulation-based training, we need to adopt conditions that represent real clinical settings and patients.

An important limitation of this study was the difference in patients between Group S and Group N. Clinical clerkship of fifth-year students was performed every 2 weeks; therefore, few patients were the same for Group S and Group N. Nevertheless, a professor from the Department of Respiratory Medicine auscultated the lung sounds from the patients and confirmed the lung sounds before professors' rounds; therefore, patients in this study appear to have been selected appropriately by the professor. One more limitation of this study is small number of students. The accurate response rate for fine crackles and coarse crackles tended to be higher in Group S than in Group N, therefore to increase number of students enrolled may lead to statistically significant of them.

We concluded that auscultation training using a simulator helped medical students differentiate abnormal lung sounds in patients. This training also improved auscultation skills but did not improve the attitudes of medical students during professors' rounds.

Acknowledgement

All authors have no COI to declare regarding the present study.

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Analysis of Gait in Stroke Patients with Hemiplegia Using a Wearable Accelerometer

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Abstract

Background

Restoration of walking ability is the major goal of rehabilitation for stroke patients with hemiplegia. However, assessment methods are based on subjective evaluation, and no established objective assessment method exists that is clinically feasible. This study aimed to determine whether accelerometers could be used as clinically feasible objective assessment tools for predicting walking ability in stroke patients with hemiplegia.

Methods

Participants included 36 stroke patients with hemiplegia who were able to walk (group C) and 40 healthy individuals (group N). Wearable accelerometers were attached at the seventh cervical (C7) and third lumbar vertebral (L3) levels. Acceleration, in three axial directions (mediolateral, vertical, and anteroposterior), was measured during walking. Root mean square values were calculated and used as indices for cervical and lumbar sway. Associations between these values and the degree of gait independence, measured using the Functional Ambulation Classification (FAC) score, were evaluated.

Results

The cervical/lumbar sway significantly increased with decreasing degrees of gait independence (from groups with FAC5 to FAC4 and FAC3) in all three directions in group C. In group N, the cervical sway was smaller than the lumbar sway in all three directions. In group C, the cervical sway increased with decreasing degrees of gait independence; however, in the group with FAC3, the cervical sway was greater than the lumbar sway, showing a reverse phenomenon.

Conclusions

These results revealed an association between body sway and degree of gait independence and

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demonstrated that evaluating cervical/lumbar sway using wearable accelerometers helped accurately and objectively assess walking ability.

Key Words: Accelerometer; Gait analysis; Hemiplegia; Functional Ambulation Classification

Introduction

It is well-known that many stroke patients with hemiplegia have abnormal gait (i.e., an abnormal walking pattern) even after they become capable of walking. Walking with an abnormal gait may lead to joint deformity and an increase in risk of falls. Therefore, it is important for stroke patients with hemiplegia to develop a normal or near-normal and stable gait as early as possible. To achieve this, an accurate and objective assessment of walking ability is needed; however, in the current clinical setting, the assessment of walking ability is based on subjective evaluation techniques, such as observation by the examiner.

In recent years, the method of using a wearable accelerometer has received attention as an objective assessment tool to predict walking ability[1]. In this method, a wearable accelerometer is typically attached to the lumbar spine near the body's center of gravity, and acceleration of the body's center of gravity is measured during walking and analyzed. However, few studies have evaluated the acceleration at regions other than the back. Although Sugawara et al reported correlations between acceleration at the cervical and lumbar spine during walking and severity of hemiplegia (i.e., impairment) in patients with stroke[2], to our knowledge, no studies have investigated the association between the acceleration of the body's center of gravity during walking and the degree of gait disturbance (i.e., disability).

This study aimed to evaluate the associations between cervical/lumbar sway during walking and walking ability using a wearable accelerometer in stroke patients with hemiplegia, and to determine whether the accelerometer could be used as a clinically feasible objective assessment tool to predict walking ability in such patients.

Methods

Participants included 36 stroke patients with hemiplegia with no evidence of joint disorder in the legs who were able to sufficiently understand the oral explanation and were able to walk along a 16-m straight course without assistance. Forty healthy individuals without gait disturbances were also included as controls. This study was approved by the ethics committee of our institution (Approval Number #1). Informed consent was obtained from each participant after full written and oral explanation of the objectives of the study and the methodologies involved.

The stroke patients with hemiplegia (group C) consisted of 29 men and 7 women, with a mean age of 69.9±9.1 years. The diagnoses were cerebral infarction in 25 patients and cerebral hemorrhage in 11 patients. Hemiplegia was right-sided in 26 patients and left-sided in 10 patients. The degree of hemiplegia, based on the Brunnstrom Recovery Stages for the lower extremities, was Ⅳ (movement deviating from basic synergies) in 8 patients, Ⅴ (movement independent of basic synergies) in 16 patients, and Ⅵ (near-normal coordinated movement) in 12 patients. The healthy individuals (group N) consisted of 26 men and 14 women, with a mean age of 27.7±7.7 years.

The degree of gait independence was rated according to the Functional Ambulation Classification (FAC) score of the Hospital at Sagunto. The FAC is a tool to evaluate functional walking ability based

Table 1. Functional Ambulation Classification (FAC)

0: Nonfunctional Ambulator	Patient cannot ambulate, ambulates in parallel bars only, or requires supervision or assistance from more than one person to ambulate safely outside parallel bars.
1: Ambulator-Dependent for Physical Assistance	Patient requires manual contact of no more than one person during ambulation on level surfaces to prevent falling. Contact is continuous and necessary to support body weight as well as to maintain balance or assist coordination.
2: Ambulator-Dependent for Physical Assistance	Patient requires manual contact of no more than one person during ambulation on level surfaces to prevent falling, consisting of continuous or intermittent light touch to assist balance or coordination.
3: Ambulator-Dependent for Supervision	Patient can ambulate without manual contact from another person but, for safety, requires standby guarding of no more than one person because of poor judgement, questionable cardiac status, or the need for verbal cuing to complete the task.
4: Ambulator-Independent, Level surfaces only	Patient can ambulate independently on level surfaces, but requires supervision or physical assistance to negotiate any of the following: stairs, inclines, or non-level surfaces.
5: Ambulator-Independent	Patient can ambulate independently on nonlevel and level surfaces, stairs and inclines.

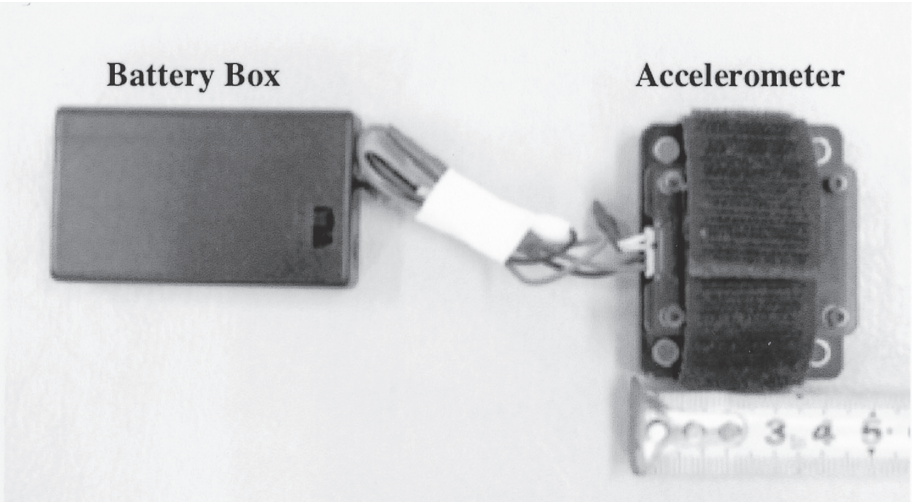

Figure 1. A wearable accelerometer, IMU-Z (ZMP Inc.), with a sensor unit size of 42.0×52.5×20.5 mm and a weight of 35g, was attached to the cervical and lumbar spine of each participant.

on observation, using a 6-point scale ranging from 0 to 5, with greater numbers indicating better walking ability[3] (Table 1). The degree of gait independence in group C was FAC3 in 6 patients (group FAC3), FAC4 in 11 patients (group FAC4), and FAC5 in 19 patients (group FAC5).

A wearable accelerometer, IMU-Z (ZMP Inc.), with a sensor unit size of 42.0×52.5×20.5 mm and a weight of 35g, was attached to the cervical and lumbar spine of each participant, and the acceleration during walking at the cervical and lumbar spine were measured. The measurements were uploaded to a computer (the host terminal) via Bluetooth, thereby allowing for a real-time measurement of acceleration without interfering with walking (Fig. 1).

The accelerometer was attached to the neck at the level of the seventh cervical vertebra (C7) and to the hip at the level of the third lumbar vertebra (L3). C7 was chosen because it is easy to identify

this vertebra tactually. L3 was chosen because it is closer to the body's center of gravity and moves in parallel with the body's center of gravity, with minimal horizontal rotation[4]. Each accelerometer was fixed using an elastic belt, and the absence of potential influence of the elastic belt on performance was confirmed by asking participants about the presence of a feeling of restraint while attaching the device every time. Participants wore their own comfortable shoes and were allowed to use a lower extremity orthosis, if needed, during the walking test; however, they were not allowed to use a cane. During the test, all obstacles that might interfere with walking were removed from the environment so that participants could concentrate on walking. In addition, for security purposes, another therapist (non-examiner) stood by the participant during the test in case of unexpected accidents. Participants walked at their preferred speed.

The walking course included two 3-m sections, each for warm-up and cool down, and a 10-m course for speed measurements, with a total of 16 m. Root mean square (RMS) values were calculated from the acceleration data in the three axial directions obtained during steady-state walking on the 10-m course. The RMS indicates the mean amplitude of the signal waveforms, and the RMS calculated from the acceleration data during walking indicates the degree of body sway during walking; higher values reportedly indicate greater sway[5-7]. The RMS value obtained from the accelerometer attached to C7 was used as the index of cervical sway, while that obtained from the accelerometer attached to L3 was used as the index of lumbar sway. The RMS value is known to be proportional to the square of walking speed, which may result in greater values. Therefore, the influence of walking speed was eliminated by dividing the obtained RMS by the square of walking speed[8]. Furthermore, the influence of body height was eliminated by dividing the value by body height.

Statistical analysis of the relationship between the degree of gait independence and the cervical/lumbar RMS values was performed using analysis of variance with a significance level of $p<0.05$. Statistical analyses were performed using statistical software [R].

Results

The mean RMS values in group N (Control) and group C (FAC 5, 4, 3) for the cervical and lumbar spine were shown in the table 2: in the mediolateral (ML) direction, the vertical (V) direction, and the anteroposterior (AP) direction, respectively. The differences were statistically significant for all items by analysis of variance (Table 2).

Furthermore, a comparison between cervical and lumbar RMS values showed that the former was lower than the latter in all three axial directions in group N, and the differences were statistically significant. In group C, the cervical RMS values increased with decreasing degrees of gait

Table 2. The RMS values in group N (Control) and group C (FAC 5, 4, 3) (mean±SD), and P values by analysis of variance.

	ML (C7)	ML (L3)	V (C7)	V (L3)	AP (C7)	AP (L3)
Control	0.034±0.008	0.049±0.013	0.069±0.010	0.087±0.022	0.037±0.010	0.068±0.021
FAC5	0.079±0.027	0.109±0.046	0.122±0.037	0.149±0.050	0.069±0.027	0.108±0.038
FAC4	0.203±0.091	0.203±0.067	0.238±0.102	0.267±0.099	0.151±0.176	0.176±0.074
FAC3	0.379±0.251	0.328±0.103	0.383±0.180	0.359±0.107	0.318±0.228	0.307±0.144
P value	3.06E-16	1.48E-21	3.29E-18	6.78E-20	2.46E-13	1.27E-15

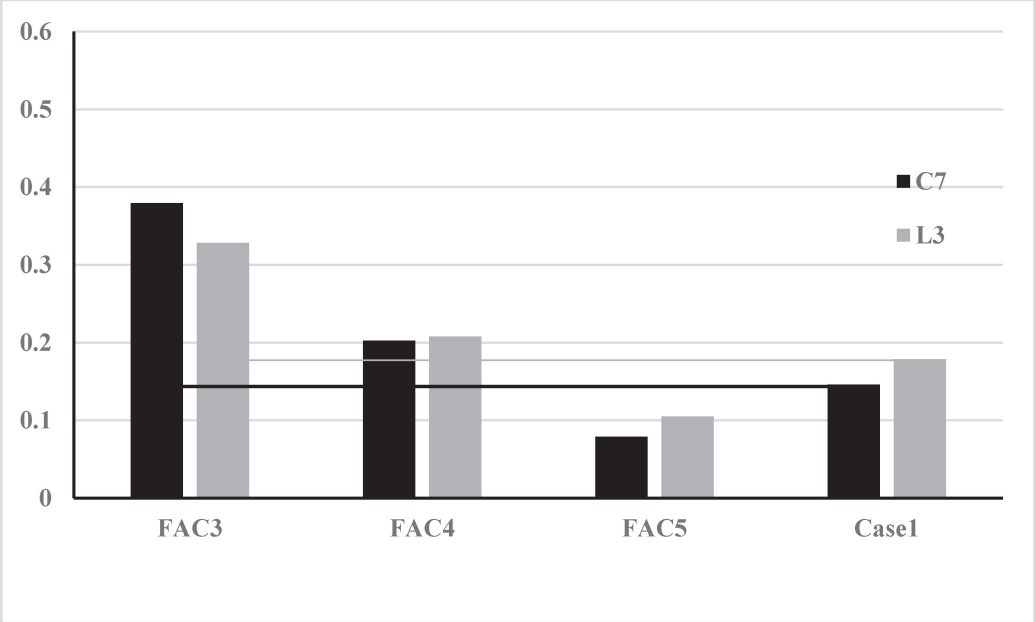

Figure 2. RMS values in ML direction of representative case are intermediate between FAC4 and FAC5, and in particular, the value of lumbar spine is close to the value of FAC4.

Table 3. FAC assessment for representative case by each therapist (* :standard)

Therapists (Years of experience)	FAC
A * (30 years)	4
B (9 years)	4
C (6 years)	5
D (5 years)	5
E (3 years)	5
F (3 years)	5
G (2 years)	4
H (2 years)	3
I (1 year)	4

independence; and cervical RMS value was higher than the lumbar RMS value in group FAC3, showing a reverse phenomenon.

Here, we report a representative case (Case 1). The patient was a 76-year-old man. He had right hemiplegia due to cerebral infarction and his Brunnstrom recovery stage for the lower extremities was Ⅴ.

The mean RMS values for the cervical and lumbar spine obtained from the accelerometer in Case 1 were as follows: in the ML direction, 0.145 and 0.178; in the V direction, 0.162 and 0.256; and in the AP direction, 0.079 and 0.133, respectively. A comparison of these values with the mean RMS values of group C (according to the FAC score) in all three axial directions showed that the RMS values of Case 1 were within±1SD of the mean RMS of group FAC4; moreover, it was lower than that of group FAC3, and outside the range of values of group FAC5. These findings suggested that the status of Case 1 corresponded to that of group FAC4 (Fig. 2 : the result in ML direction).

Furthermore, the degree of gait independence of representative case was evaluated by 10 physical therapists (the mean work experience duration was 6.2 years, ranging from 1 to 30 years) using the FAC score. Although there were variations among therapists in terms of the results, the patient status was rated as FAC4 by all physical therapists with sufficient experience. Thus, the result obtained from the RMS values coincided with that obtained from physical therapists with sufficient experience (Table 3).

Discussion

Walking is an extremely complex movement. Bipedal locomotion—walking on two legs in an upright position—is a dynamic repetitive movement with a regular pattern, in which the lost balance is restored by using two legs alternatively. To achieve walking, control of the trunk (central part of the body) is necessary; thus, stability of the trunk is important for achieving smooth movement of the upper and lower extremities. It is therefore considered that decreased trunk function leads to decreased walking ability. In addition, the anatomical structure for controlling trunk motion is extremely complex[9].

The results of this study showed that body sway during walking (both cervical and lumbar spine) significantly decreased with increasing degrees of gait independence in all three axial directions (ML, V, and AP). The findings showed an association between body sway during walking and walking ability.

In group N, the cervical sway was significantly smaller than the lumbar sway in all three axial directions. In group C, the cervical sway increased with decreasing degrees of gait independence; moreover, in group FAC3, the cervical sway was greater than the lumbar sway, showing a reverse phenomenon. The results showed that the characteristic features of body sway in group FAC3 were different from those of healthy individuals. Increased cervical sway in group FAC3 was considered one of the reasons for these patients requiring stand-by assistance.

FAC3 is described as follows: "Patients can walk independently on level ground but require stand-by help from one person for security purposes (walking with stand-by assistance)"[2]. A study in healthy elderly individuals using a motion sensor indicated a significant difference in the displacement range of body sway during walking between the lower part of the trunk and the head, and that the trunk sway was attenuated in the process of its transmission to the head. The findings support the notion that the higher cervical sway in comparison to the lumbar sway in group FAC3, in contrast to the pattern observed in healthy individuals, was one of the reasons for these patients requiring stand-by assistance while walking.

Group FAC4/FAC5 showed smaller cervical/lumbar sway in comparison to group FAC3; moreover, in contrast to group FAC3, group FAC4/FAC5 showed smaller cervical sway than lumbar sway—a body sway pattern similar to that of healthy individuals. We believe that the decrease in cervical/lumbar sway, as well as the relative decrease in cervical sway compared with lumbar sway, leads to an improvement in safety and independence of gait.

In general, walking ability is assessed by observing walking behavior and by detecting the presence/absence of abnormal gait pattern. Observational assessment of walking can yield acceptable results if it is performed in a systematic manner; however, detailed measurements may be inconsistent among examiners[9]; some researchers may consider that the inter-rater reliability is low owing to the differences in "observational perspective" and "subjective scale".

This study showed that cervical/lumbar sway during walking, measured using a wearable accelerometer, significantly differed according to the degree of gait independence. It was demonstrated that the evaluation of cervical/lumbar sway using the wearable accelerometer allows accurate and objective assessment of walking ability, and the wearable accelerometer can be used as a clinically feasible, objective assessment tool.

Some limitations of the study must be considered while interpreting the study results. There was a large difference in the mean age of group C (stroke patients with hemiplegia) and group N (healthy individuals), which may have influenced the results. Walking ability, and dynamic and static balance are reportedly reduced in older people compared with younger people[10,11]. Further studies using an age-matched control group are needed. In addition, the time dependent changes in the degree of gait independence in stroke patients with hemiplegia were not examined in this study, and further study of this issue is also needed.

This study evaluated the associations between cervical/lumbar sway during walking and the degree of gait independence using a wearable accelerometer in stroke patients with hemiplegia.

The cervical/lumbar sway significantly increased in all three axial directions (ML, V, and AP) with decreasing degrees of gait independence [from group FAC5 (completely independent) to FAC4 (independent only on plain ground) and FAC3 (walking with stand-by assistance)] in both group C (stroke patients with hemiplegia) and group N (healthy individuals). Furthermore, the cervical sway increased with decreasing degrees of gait independence; in addition, in group FAC3, the cervical sway was greater than the lumbar sway, showing a reverse phenomenon.

The results from this study revealed associations between cervical/lumbar sway during walking and the degree of gait independence, and demonstrated that the wearable accelerometer could be used as a clinically feasible objective assessment tool for predicting walking ability.

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Finite Time Span of High-intensity Signal on T1-weighted Magnetic Resonance Imaging Produced by a Human Blood Clot Using a Circulating Vessel Phantom System

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Abstract

Background

Following the introduction of non-contrast T1-weighted imaging (T1WI) in magnetic resonance imaging, using the inversion-recovery gradient-echo sequence, many researchers have shown that high-intensity signals (HISs) in carotid and coronary arterial walls indicate the presence of intraplaque hemorrhage or intracoronary thrombus containing methemoglobin. However, the time span of HISs generated by thrombus remains unknown. The aim of this study was to image a circulating vessel phantom with T1WI to determine if flow disturbance causes artifacts, such as a HIS and to perform serial observations of a human blood clot.

Methods

Vessel bifurcation models were created using Y-type tube joints made of polypropylene, with and without stenosis or occlusion with a human blood clot or non-magnetic material. Our circulating vessel phantom consisted of five parts, namely, a non-pulsatile pump, a fluid reservoir, silicone tubes, a vessel surrounding a human myocardium-equivalent phantom, and human blood-equivalent fluid. We evaluated T1WI using this system.

Results

On T1WI, the areas surrounding the bifurcations with stenosis or occlusion with non-magnetic material showed no HISs. However, a HIS was found at the site of occlusion with a blood clot. The signal intensity of the blood clot increased, as compared with the baseline, at 1 and 3 months, subsequently decreasing at 4 months and then disappearing at 5 months.

Conclusions

This phantom study showed that a human blood clot generated a HIS on T1WI without being affected by blood flow blood, and the presence of the signal was limited to a finite time span of <5 months.

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Key Words: Magnetic resonance imaging; Atherosclerotic plaque; Thrombosis; Phantom; Coronary artery

Introduction

Advances in the field of magnetic resonance (MR) imaging have allowed for non-invasive, *in vivo* assessment of human carotid[1-5] and coronary atherosclerotic plaques[6-14]. Following the introduction of non-contrast T1-weighted imaging (T1WI), using inversion-recovery gradient-echo sequence with black-blood condition, many researchers have shown that high-intensity signals (HISs) in the carotid and coronary arterial walls indicate the presence of intraplaque hemorrhage or intracoronary thrombus containing methemoglobin[2-8,10] and relate to future cardiovascular events[9,11,12]. Furthermore, some studies have demonstrated that MR imaging can identify not only the presence of a thrombus or hemorrhage but also its stage of development in patients with deep vein thrombosis[15], pulmonary embolism, and complex carotid plaques[4,16]. However, the time span of HIS generated by thrombus remains unknown.

The T1WI MR technique overcomes many difficulties associated with conventional techniques that generated a signal based on blood flow. With T1WI, signal generation does not rely on flowing blood because it uses a non-slice-selective inversion recovery pulse for the black-blood method. Further, image interpretation requires only the detection of a high signal, rather than visualization of the unaffected vessel wall[17]. Although theoretically the T1WI technique is considered to be unaffected by blood flow, this supposition has not been verified with actual clinical images.

Understanding the progression of the HIS from thrombi will ultimately require serial observations with T1WI in MR. A circulating vessel phantom system is useful for observing and monitoring the development and disappearance of HISs produced by thrombi. It can also be used for assessing the effects of flowing blood on the HIS with T1WI. The aims of this study are to verify whether flow disturbance causes artifact like an HIS and to perform a serial observation of human blood clots, using a circulating vessel phantom system with T1WI in MR.

Methods

The study was approved by the Osaka City University Hospital' s ethics committee.

Production of vessel bifurcation models with stenosis or occlusion

Four types of vessel bifurcation models were created with Y-type tube joints made of polypropylene (width 3.2×inner diameter 0.65×height 5.0 cm; #PP-PY-S: AS ONE Co., Osaka, Japan). The first model consisted of a bifurcation with total occlusion with human venous blood clot in one side branch, using blood obtained from a volunteer and coagulated at room temperature (Fig. 1A). The second model consisted of occlusion formed by resin (non-magnetic material) in one side branch (Fig. 1B). The third model involved severe stenosis formed by resin in one side branch (Fig. 1C), and the fourth contained no stenosis or occlusion (Fig. 1D). Silicone tubes were connected to each end of the coronary bifurcation models and then passed through the plastic container (diameter: 167 mm; capacity: 3.2 liters) (Fig. 1).

Preparation for human blood-equivalent fluid and human myocardium-equivalent phantom

For MR imaging, the recognized T1 and T2 values in a 1.5T are approximately 1500 ms and 200 ms for the blood[18], and around 950 ms and 50 ms for the myocardium[19], respectively.

In our study, we first prepared a human blood-equivalent fluid. To prepare 10000 mL of

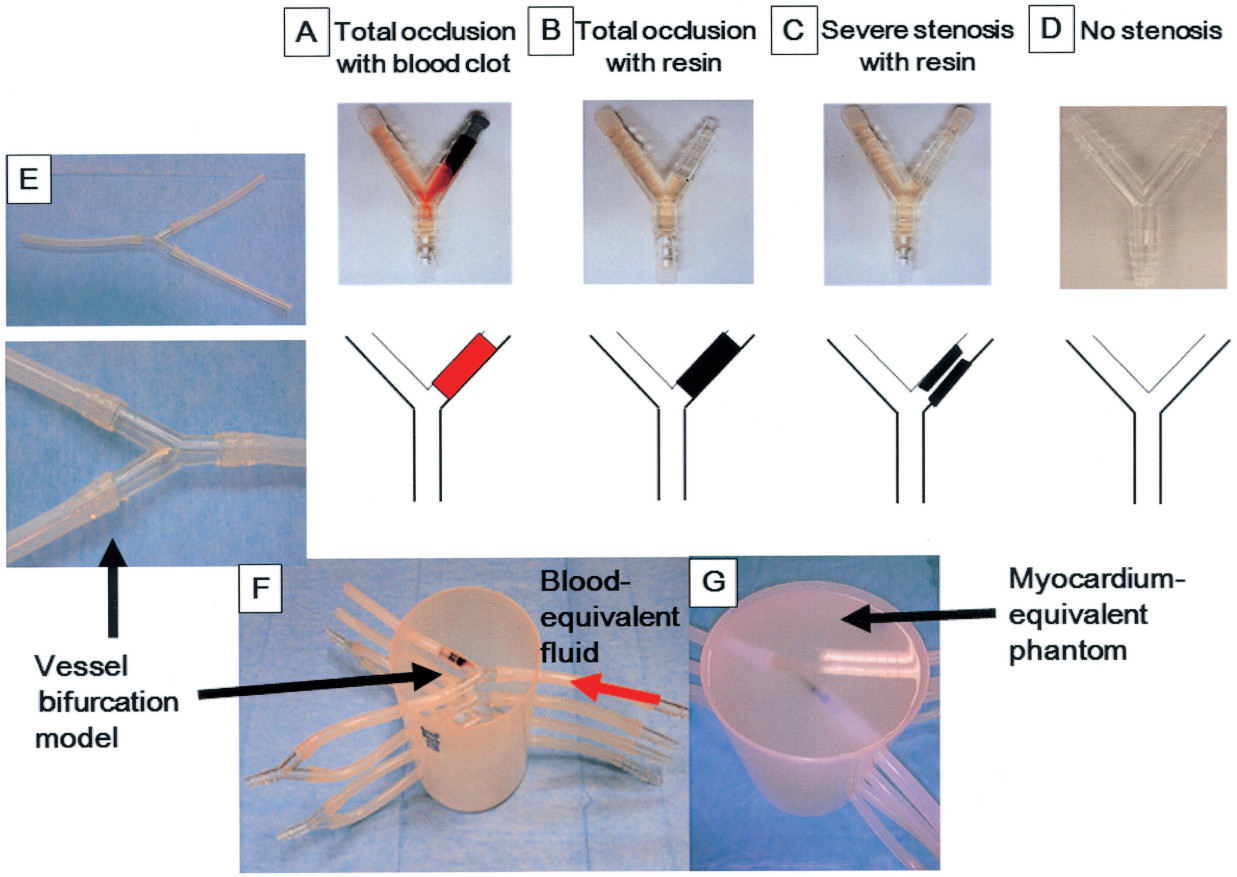

Figure 1. Four types of vessel bifurcation models with and without concentric stenosis or occlusion. A, Total occlusion using a human blood clot in one side branch. B, Total occlusion formed by non-magnetic material in one side branch. C, Severe stenosis formed by non-magnetic material in one side branch. D, No stenosis or occlusion. E, Silicone tubes were connected to each end of the coronary bifurcation models. F, These tubes were passed through a plastic container. G, A human myocardium-equivalent phantom, consisting of the dissolved agarose solution, was poured into the prepared plastic container, and cooled to room temperature for solidification.

circulating fluid to approximate the relaxation times of blood, we mixed 1000 mL of Manganese Chloride Tetrahydrate (Bothdel Oral Solution 10; Meiji Dairies Co. and Kyowa Hakko Kirin Co., Ltd, Tokyo, Japan) into 9500 mL of saline.

We then created a human myocardium-equivalent phantom using agarose powder (Type 1, low EEO, #A-6013: SIGMA-ALDRICH, St. Louis, USA) as a gelling agent, Meglumine Gadopentetate (Magnevist; Bayer HealthCare, Berlin, Germany) as the T_1 modifier, Manganese Chloride Tetrahydrate (Bothdel Oral Solution 10; Meiji Dairies Co. and Kyowa Hakko Kirin Co., Ltd, Tokyo, Japan) as the T_2 modifier, NaN3 (Katayama Chemical, Osaka, Japan) as an antiseptic, and physiological saline. To prepare a 3800g myocardium-equivalent phantom, we used 39.2g of agarose powder (1.15%), 0.5 mL of Meglumine Gadopentetate, 357.9 mL of Manganese Chloride Tetrahydrate, 1.13g of NaN_3 (0.03%), and 3400 mL of saline, as described in a previous report[20,21]. These ingredients were mixed in a stainless steel pot and constantly stirred, while heated using an induction heating apparatus. The heating continued until the agarose powder was dissolved, and a clear solution was obtained. The agarose powder dissolved at 40℃ for 70 min, and heating continued for 80 min and then stopped. The maximum temperature of the solution reached 70℃, and stirring continued until

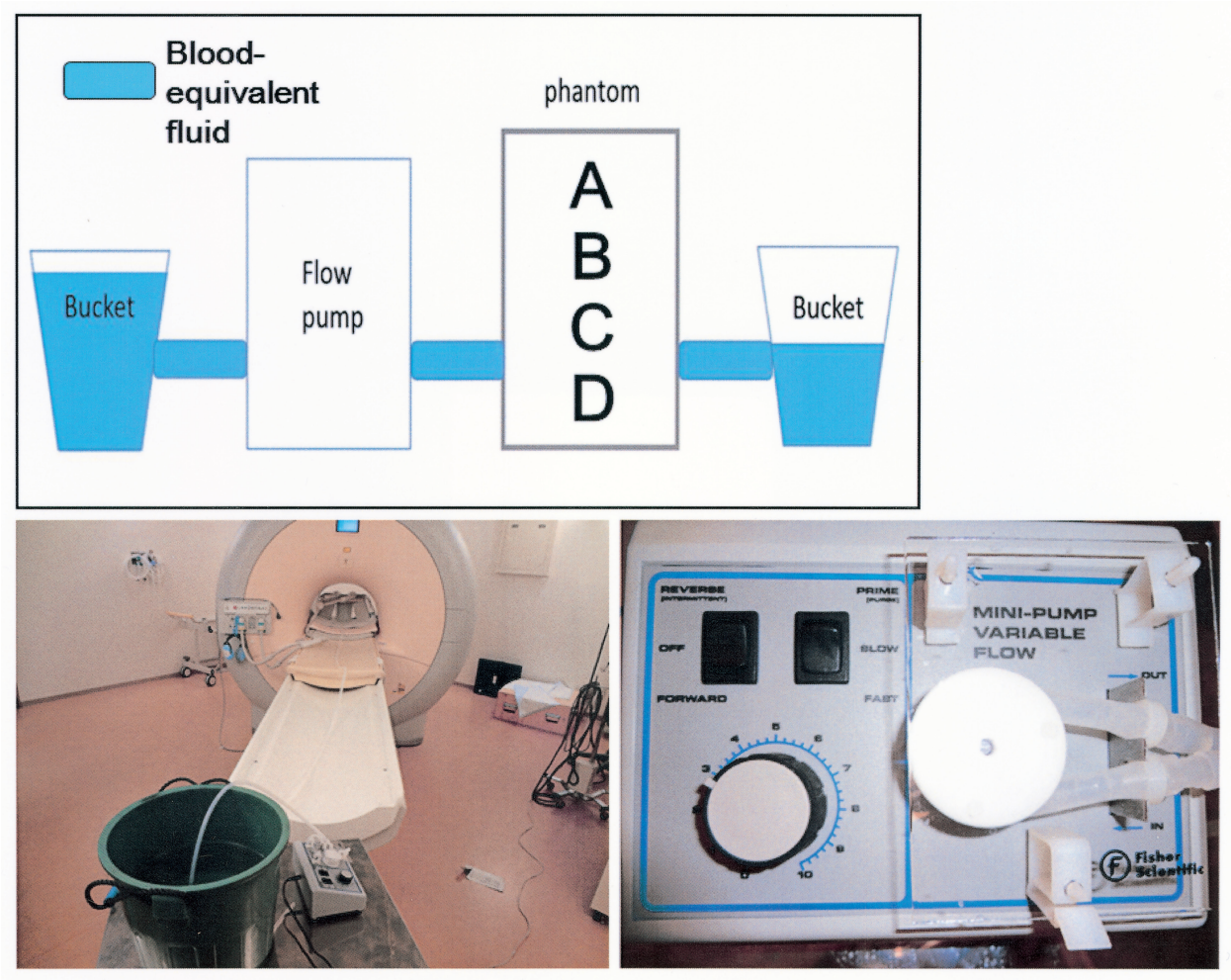

Figure 2. Circulating vessel phantom system.

100 min.

Finally, the agarose solution was slowly poured into the prepared plastic container, equipped with the previously mentioned coronary bifurcation models, and cooled to room temperature for solidification (Fig. 1).

Circulating vessel phantom system

Our circulating vessel phantom system consisted of five parts forming a closed circuit: a non-pulsatile pump, a fluid reservoir, 8-mm inner diameter silicone tubes, a vessel phantom surrounding a human myocardium-equivalent phantom, and human blood-equivalent fluid (Fig. 2). The mean velocity of the human blood-equivalent fluid was adjusted to 15-17 cm/s within the circulating vessel phantom system, using a non-pulsatile pump[22]. This phantom was preserved in room air.

MR image acquisition

Phantom MR imaging was performed using a 1.5-T MR system (Philips Healthcare, Best, The Netherlands) with a 32-elements cardiac coil. Images were obtained at baseline and once monthly for up to eight months after collection of the human blood sample. Initial survey images were focused around the phantom, and reference images were then obtained to assess the sensitivity of parallel imaging. First, a phase-contrast turbo gradient echo technique (Q-FLOW) was used to measure flow velocity within the circulating vessel phantom system[23]. Next, to confirm the flow status through the

stenosis or occlusion, steady-state free precession three-dimensional MR angiographic images were acquired (repetition time, 3.7 ms; echo time, 1.8 ms; flip angle, 80°; SENSE factor, 2.0; number of excitations, 1; acquisition trigger delay, 632 ms; field of view, 250×250×53 mm; acquisition matrix, 202×202; reconstruction matrix, 480×480×105, resulting in an acquired spatial resolution of 1.25×1.25×1.5 mm, reconstructed to 0.52×0.52×0.75 mm). Then, black-blood images at baseline were obtained using a three-dimensional T1WI inversion-recovery gradient-echo sequence with a Look Locker sequence, fat-suppressed and radial k-space sampling in Y-Z plane (repetition time, 4.4 ms; echo time, 2.0 ms; flip angle, 20°; SENSE factor, 2.5; number of excitations, 2; TFE pre-pulse consisted of non-selective and adiabatic inversion pulses; TFE prepulse inversion time, 400 ms; acquisition trigger delay, 600 ms; field of view, 250×250×42.5 mm; acquisition matrix, 187×187; reconstruction matrix, 448×448×85, resulting in an acquired spatial resolution of 1.34×1.34×1.7 mm, reconstructed to 0.56×0.56×0.85 mm)[8,10,12]. As these sequences need to recognize R waves, the phantom was imaged at a cardiac frequency of 60 bpm, using a simulated electrocardiogram. From one month after the collection of the human blood sample onward, imaging of the surrounding human myocardium-equivalent phantom without circulating human blood-equivalent fluid was performed using a three-dimensional T1WI inversion recovery gradient-echo sequence, fat-suppressed and linear k-space sampling in Y-Z plane (repetition time, 7.9 ms; echo time, 3.6 ms; flip angle, 12°; SENSE factor, 2.0×2.0; number of excitations, 1; TFE prepulse, invert; TFE prepulse inversion time, 1100 ms; field of view, 220×220×220 mm; acquisition matrix, 220×220; reconstruction matrix, 432×432×220, resulting in an acquired spatial resolution of 1.0×1.0×1.0 mm, reconstructed to 0.51×0.51×1 mm).

Measurements of the T1 and T2 relaxation times for the blood-equivalent fluid and the human myocardium-equivalent phantom were made by MIXED sequence[24].

MR signal intensity analysis

The areas around the bifurcations with stenosis and total occlusion were analyzed. When an HIS was visually confirmed on T1WI, signal intensity at the proximal and distal parts of the signal was measured.

The target area within the vessel model-to- myocardial phantom signal-intensity ratio, defined as the highest signal intensity of the target area within the vessel model divided by the signal intensity of the myocardial phantom, was calculated by placing a freehand circular region of interest on a standard console of the clinical MR system[6-14].

Results

Using a 1.5T MR scanner, the T1 and T2 values of the blood-equivalent fluid were 1342 ms and 183 ms, and those of the human myocardium-equivalent phantom were 962 ms and 130 ms, respectively. These values were similar to recognized values in the literature. Figure 3 shows the baseline MR angiography and T1WI for each vessel bifurcation model. Vessel occlusion or stenosis within the bifurcation models was confirmed by MR angiography. On T1WI, the areas around the bifurcations with stenosis or total occlusion formed by resin show no HISs (Figs. 3B-3D). However, a HIS was found at the site completely occluded with a human blood clot (Fig. 3A).

Table 1 shows the time course of signal intensity from the proximal and distal parts of the human blood clot and myocardial phantom during the follow-up period. The signal intensity of the human blood clot at one and three months increased compared with that at baseline, and subsequently

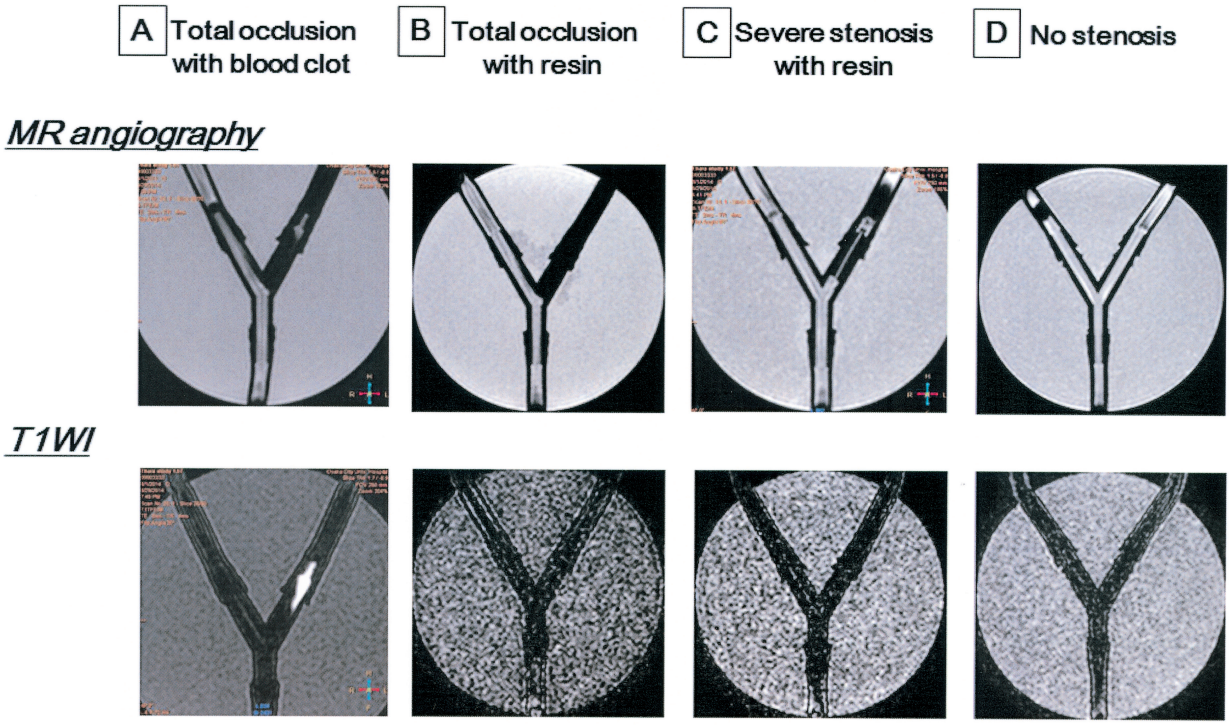

Figure 3. Baseline MR angiography and T1WI for each vessel bifurcation model.

Table 1. Time course of signal intensity of the proximal and distal parts of the human blood clot and myocardial phantom

	Proximal part			Distal part		
	Thrombus	Myocardial phantom	Signal-intensity ratio	Thrombus	Myocardial phantom	Signal-intensity ratio
Baseline	163.40	115.67	1.41	146.33	114.65	1.28
1 month	163.41	106.85	1.53	234.13	118.99	1.97
3 month	196.12	103.54	1.89	192.83	119.76	1.61
4month	119.65	95.09	1.26	163.08	122.49	1.33
5 month	4.94	109.66	0.05	3.44	146.51	0.02
6 month	4.35	123.89	0.04	2.50	154.67	0.02
7 month	3.59	121.41	0.03	4.58	147.52	0.03
8 month	3.35	120.11	0.03	3.11	151.92	0.02

decreased at four months. The signal disappeared at five months after the collection of the human blood sample, and remained at low levels. In contrast, the signal intensity of the myocardial phantom slightly increased during the follow-up period. As shown in Figure 4, an increase in the human blood clot-to-myocardial phantom signal-intensity ratio was observed at one month compared with that at the baseline. The signal then decreased at four months, and disappeared completely by five months at both the proximal and distal parts (proximal part; baseline: 1.41, one month: 1.53, three months: 1.89, four months: 1.26, five months: 0.05, six months: 0.04, seven months: 0.03, and eight months: 0.03, distal part; baseline: 1.28, one month: 1.97, three months: 1.61, four months: 1.33, five months: 0.02, six months: 0.02, seven months: 0.03, and eight months: 0.02).

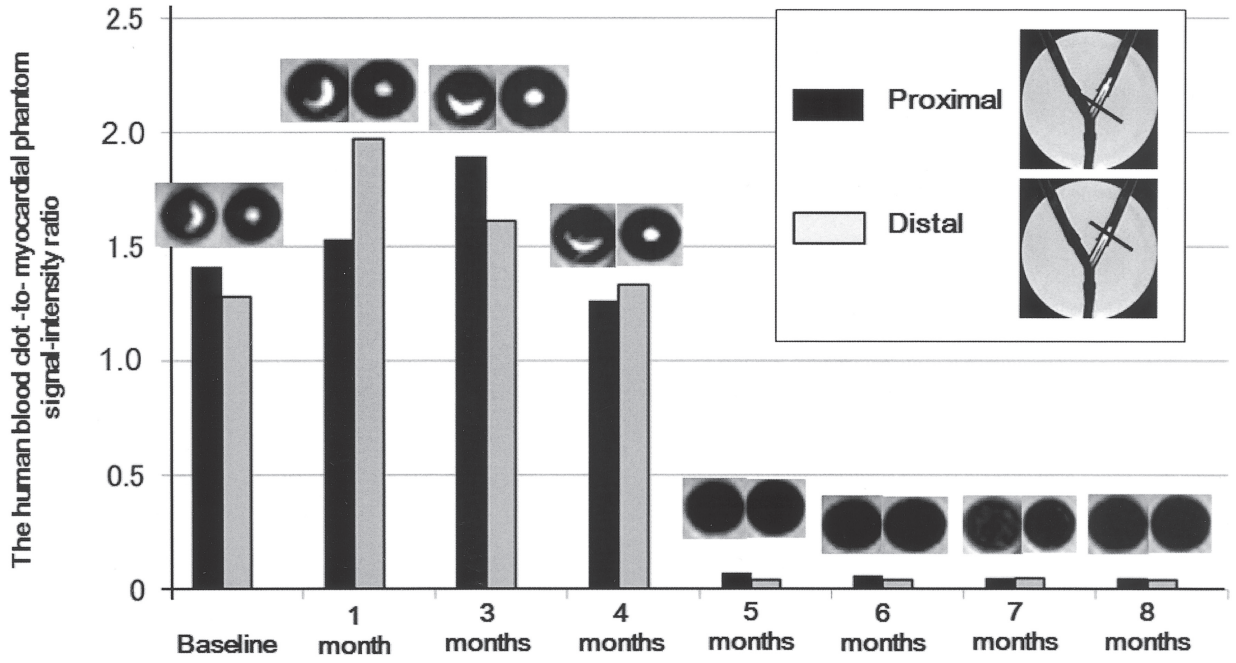

Figure 4. Time course of the human blood clot-to-myocardial phantom signal-intensity ratio in the proximal and distal parts.

Discussion

This phantom study with T1WI in MR has three major findings. First, flow disturbance did not cause an artifact HIS. Second, a human blood clot did generate an HIS. Finally, the HIS generated from a human thrombus on T1WI was limited to a time span of less than several months.

MR technology enables assessment of the atherosclerotic plaque morphology *in vivo*. It has been reported that HISs of the carotid and coronary arteries on T1WI indicate the presence of intraplaque hemorrhage or intracoronary thrombus containing methemoglobin[2-8,10]. Recently, we demonstrated that intraluminal and intrawall HISs on T1WI in angina patients are related to the different types of vulnerable plaque morphology[10]. Intraluminal HISs were associated with thrombus and intimal vasculature assessed using optical coherence tomography, while macrophage accumulation and absence of calcification were independent factors associated with intrawall HISs. Interestingly, the percent diameter stenosis was significantly greater in lesions with intraluminal HISs than in non-HIS lesions. Recently, our different study investigated the association between the duration of coronary occlusion and HIS on T1WI in MR among patients showing total coronary occlusion on angiography. We demonstrated that HISs were found frequently on the proximal edge of the occlusion[14]. From these data, we hypothesized that the HIS on T1WI might arise not only from methemoglobin but also from static or turbulent blood flow in severely stenotic or occluded coronary lesions. The T1WI technique is theoretically unaffected by blood flow, because it uses a non-selective inversion-recovery pulse for a black-blood condition. The inversion time for a null blood condition using a Look Locker sequence was determined by adjusting the flow of blood. The HIS may have resulted from a gap in a null point, since the longitudinal magnetization of stagnant blood is less than that of flowing blood. We now developed a circulating phantom system to verify whether flow disturbances cause artifact like an HIS. Our results show that the areas around bifurcations with

stenosis or total occlusion formed by non-magnetic material show no HISs on T1WI. These findings lead us to conclude that the T1WI technique is not affected by various blood flow patterns in accordance with a previous report[17].

Furthermore, studies have demonstrated that the presence of an HIS on non-contrast T1WI had the potential to predict the stage of a thrombus *in vivo*[4,15,16]. Kelly et al reported that red blood cells containing methemoglobin produced T1 shortening in proportion to the amount of methemoglobin[17]. They also supposed that this signal persists for several weeks, though the overall period is less than six months. Our recent MR study regarding coronary total occlusion revealed that the frequency of an HIS within the occlusion site was significantly higher in short duration occlusions, estimated to be less than six months, than in long duration occlusions[14]. In this phantom study, the HIS on T1WI generated from a human blood clot was limited to a span of less than several months. These *in vivo* data, together with our present *in vitro* findings, support the conclusion that the HIS on T1WI was associated with the presence of a recent thrombus, and the signal would be limited to a finite time span.

Such information on thrombus age may have several novel clinical implications in the field of coronary intervention, including the prediction of slow-flow/no-flow phenomena or the determination of the age of a chronic total occlusion. The precise assessment of recent plaque thrombosis or hemorrhage could be useful in the identification of lesions at high-risk for no-reflow to deploy distal protection devices and may influence procedural success rates for chronic total occlusion, which could lead to more appropriate risk-stratification and treatment[25,26]. Additionally, Noguchi et al reported that statin therapy reduced the coronary plaque-to-myocardium signal-intensity ratio, as well as low-density lipoprotein cholesterol and high-sensitivity C-reactive protein levels[13]. If statin therapy not only modifies plaque morphology and makes it more stable, but also accelerates the degradation of methemoglobin, it could be invaluable in treatment strategies for atherosclerosis.

This study has several limitations. First, in our circulating vessel phantom system, the non-pulsatile pump and human venous blood were used. Degeneration of blood clot depends on various intraplaque environments *in vivo*, such as temperature, surrounding tissue, and oxygen pressure. Methemoglobins are formed by oxidization of deoxyhemoglobins in a suitable oxygen pressure. Therefore, the human clot formed and preserved at room temperature *in vitro* might have a different appearance or time course on MR than intraplaque hemorrhage or juxtaluminal thrombus *in vivo*. Second, the human myocardium-equivalent phantom made of gel may degenerate in months, and the relaxation times of that may change at each observational point.

This circulating vessel phantom study showed that a human blood clot generated a HIS on T1WI, without being affected by flowing blood, and this signal was limited to a finite time span less than several months. This circulating vessel phantom system was useful for serial observation and monitoring of the development or disappearance of HIS produced by thrombi and for verification of the effect of flowing blood on HIS with T1WI.

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Identification of Factors Predicting the Onset of Gallbladder Cancer Complicated with Pancreaticobiliary Maljunction

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Abstract

Background

Pancreaticobiliary maljunction (PBM) is a congenital anomaly in which bile and pancreatic juice flow into each other and is well known to promote carcinogenesis. Further, carcinogenesis has a wide age range, from early childhood to old age. It is believed that differences in the confluence form, such as the junction angle θ between the bile duct and pancreatic duct, and the cross-sectional area of each lumen is strongly affected. We aimed to identify predictive factors of carcinogenesis.

Methods

We measured several confluence form parameters and examined differences between patients with and without gallbladder (GB) cancer who underwent surgery at our hospital.

Results

The cosine of θ (cosθ), junctional bile duct cross sectional area (Cb), and shape of the common bile duct {ratio of the maximum diameter of the congenital biliary dilatation to the diameter of the bile duct [MCBD/Db]} significantly differed between the groups.

Conclusions

We defined several cut-offs predicting the carcinogenesis of GB cancer as follows:

(1) $\cos\theta \geqq 0.84$, (2) $Cb \geqq 8.0$, and (3) $MCBD/Db \leqq 4.3$.

While it is impossible to measure the degree of reciprocal flow of bile and pancreatic juice in vivo, these cutoff values can be important indicator of the risk of GB carcinogenesis in PBM cases.

Key Words: Biliary tract neoplasms; Carcinogenesis; Pancreatic juice; Common bile duct; Pancreatic ducts

Introduction

Pancreaticobiliary maljunction (PBM) is a congenital anomaly in which the pancreatic and bile

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ducts merge outside the duodenal wall, and bile and pancreatic juice flow into each other because the sphincter of Oddi does not control the junction[1]. The reflux of pancreatic juice into the biliary tract provokes higher rates of biliary tract cancer[2-5] and is its most important prognostic factor. According to the results of a nationwide survey[6], bile duct and gallbladder cancers were found in 6.9% and 13.4% of adult patient with PBM, respectively. Biliary tract cancers develop about 15-20 years earlier in patients with PBM than in individuals without PBM. The carcinogenesis of biliary tract cancer accompanying PBM is considered to involve a hyperplasia-dysplasia-carcinoma sequence induced by chronic inflammation caused by bile and pancreatic juice flow into each other, which is different from the adenoma-carcinoma sequence or the de novo carcinogenesis associated with biliary tract cancers in patients without PBM. It is well known that the time of carcinogenesis varies widely from early childhood to old age[7-9]. This suggests that there are important factors controlling the appearance of carcinogenesis. Since PBM is a confluence phenomenon of the biliary tract and pancreatic duct, it is appropriate to quantify it with hydrodynamic considerations. However, to our knowledge no previous study has used a fluid dynamics approach to understand PBM.

Furthermore, biliary tract cancer has poor prognosis, and it is very useful to predict carcinogenesis in cases of PBM and to start treatment before carcinogenesis. We therefore studied PBM using a confluence model that considers two viscous fluids, bile and pancreatic juice, as a new hydrodynamics approach[10,11], and we aimed to identify predictive factors of carcinogenesis.

Methods

Patients

Among 91 patients with PBM who underwent hepaticojejunostomy between September 1990 and September 2017 at our hospital, we studied 37 patients for whom clear medical image findings and test results were available. We focused on the carcinogenesis of gallbladder (GB) cancer, and patients were grouped by whether they had GB cancer or not.

The clinical records, laboratory test results, and clear medical image findings of magnetic resonance cholangiopancreatography and abdominal computed tomography, which are pressure-free images of the biliary tract, were reviewed.

The local ethics committee approved this study (authorization number, 4013).

Parameter calculations

To consider PBM as a confluence of two viscous fluids, the key points to explain the phenomenon precisely are the flow quantity (including the lumen cross-section), junction angle, and lumen form. We set the following parameters to examine the confluence of PBM: diameters of the bile duct and pancreatic duct at the junction site, length of the common channel, maximum diameter of the congenital biliary dilatation (MCBD), and the ratio of MCBD to bile duct diameter at the junction site (MCBD/Db). Figure 1 visually illustrates these parameters. Additional parameters included in the model were the angle (θ) formed from the lines extending from the pancreatic and bile ducts, cross sections of the pancreatic and bile ducts at the junction site, and amylase in the gallbladder (AMY).

The bile duct cross-sectional area (Cb) and pancreatic duct cross-sectional area (Cp) were calculated as follows:

$Cb = \pi (Db / 2)^2$, $Cp = \pi (Dp / 2)^2$,

Where Db and Dp are the diameters of the bile and pancreatic ducts at the junction site, respectively.

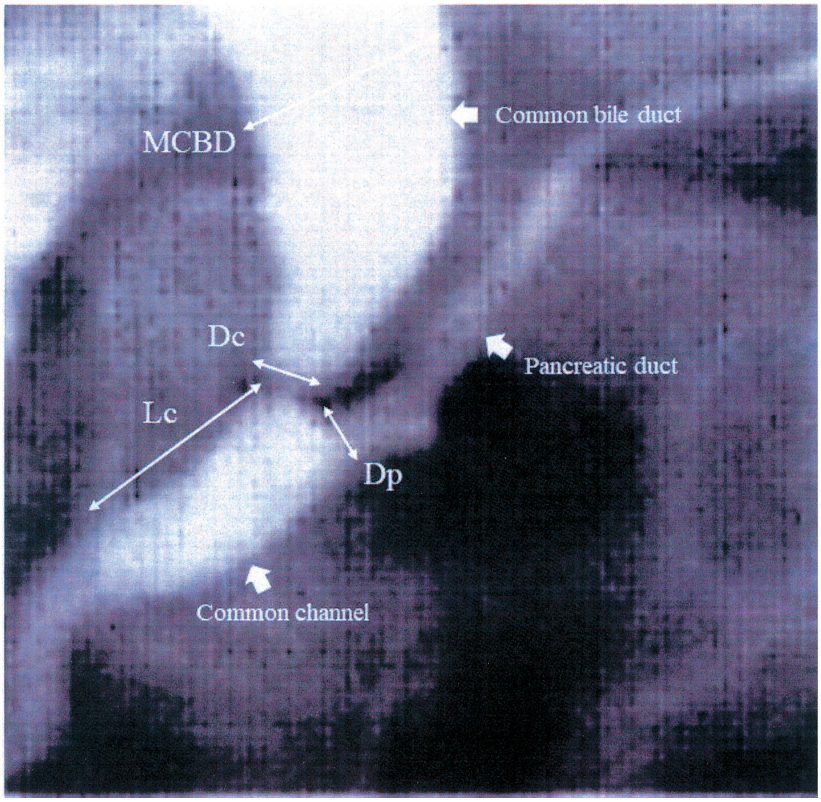

Figure 1. Parameters chosen to examine the confluence of pancreaticobiliary maljunction. MCBD, maximum diameter of the congenital biliary dilatation; Db, diameter of the biliary duct; Dp, diameter of the pancreatic duct; and Lc, length of the common channel.

The trigonometric function cosθ was calculated as follows:

(1) We draw a line crossing both extension lines from the bile duct and pancreatic duct, and make a triangle.

(2) We define the lengths of the triangle forming θ as a and c, and the length of the intersection is defined as b.

(3) We measure each length five times and calculate the average.

(4) Using the average values from step (3), we calculated cosθ as follows:

$$\cos\theta = (a^2 + c^2 - b^2) / 2ac \quad (-1 \leqq \cos\theta \leqq 1)$$

Figure 2 visually illustrates θ and cosθ to make them easier to understand, and the parameters mentioned above for the confluence of two viscous fluids are summarized in Table 1.

It is believed that free reflux of pancreatic juice into the biliary tract and gallbladder can induce chronic damage to them, and eventually cause biliary carcinogenesis. Because AMY is representative of the refluxing pancreatic enzymes, we were interested in the relationship between AMY and other parameters at the confluence of PBM. Therefore, we performed a correlation analysis between them.

Statistical analysis

Normally distributed continuous data were expressed as the mean±standard deviation (SD). Continuous variables were examined using the Mann-Whitney U test. Differences were considered significant at the level of $p<0.05$.

Spearman's rank correlation coefficient test was used to examine correlations between parameters, while the GB carcinogenic rate for each type was analyzed using the Chi-square test for independence.

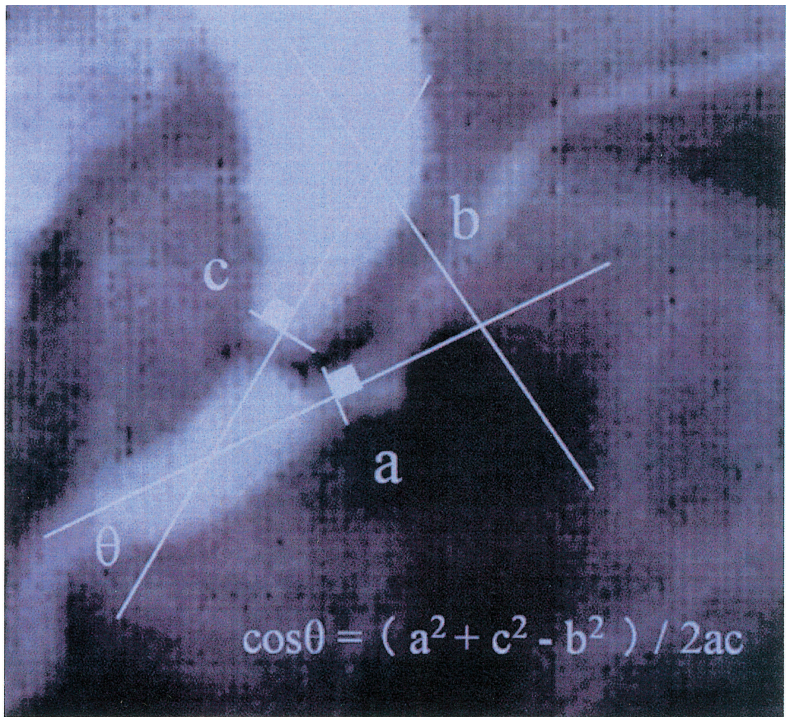

Figure 2. Visual illustration of θ, cosθ and three side lengths of the triangle a, b, and c.

Table 1. Parameters characterizing the fluid junction

Parameter	Abbreviation
Bile duct diameter	Db
Pancreatic duct diameter at juntion	Dp
Angle formed from the two extension lines	θ
Trigonometric function for θ	cosθ
Length of common channel	Lc
Bile duct cross section	Cb [= π (Dc /2)^2]
Pancreatic duct cross section	Cp [= π (Dp /2)^2]
Widest diameter of the choledochal cyst	MCBD
Proportion of the choledochal cyst	MCBD/Db
Amylase in the gall bladder	AMY

Data were analyzed using JMP, version 13 (SAS Institute Inc. Cary, NC, USA).

Results

Of 37 cases, there were 10 cases with GB cancer and 27 without. Table 2 presents the clinical characteristics between the groups. There was no significant difference except surgical age. Eleven cases were type Ⅰa, 15 were type Ⅰc, and 11 were Ⅳ-A, according to the Todani classification[1]. Figure 3 shows the age distribution of each type. The surgical age range was wide, and all types were observed in patients with GB cancer. Figure 4 shows the average surgical age for patients without GB cancer. There was no significant difference between types.

Figure 5 shows that the carcinogenic rate clearly differs between each type ($p=0.012$). Table 3 presents the comparisons of these parameters between patients with and without GB cancer. For

Table 2. Comparison of patients' characteristics

Variable	GB cancer Yes (n=10)	GB cancer No (n=27)	p value
Surgical age	56±10	17±18	<0.001
Male:female	2:08	9:18	0.47
Biliary calculus	2/10 (20%)	11/27 (40.7%)	0.34
AST U/L	95±182	101±167	0.79
ALT U/L	109±232	74±107	0.53
γGTP U/L	206±367	142±240	0.36
ALP U/L	541±860	719±151	0.34
T-Bil mg/dL	1.35±1.07	1.63±3.09	0.37
D-Bil mg/dL	0.65±0.89	0.51±0.92	0.5
LDH U/L	287±124	396±282	0.5
WBC /μL	6475±1817	8071±4239	0.37

GB, gallbladder; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γGTP, gamma-glutamyl transferase; ALP, alkaline phosphatase; T-Bil, total bilirubin; D-Bil, direct bilirubin; LDH, lactate dehydrogenase; and WBC, white blood cells.

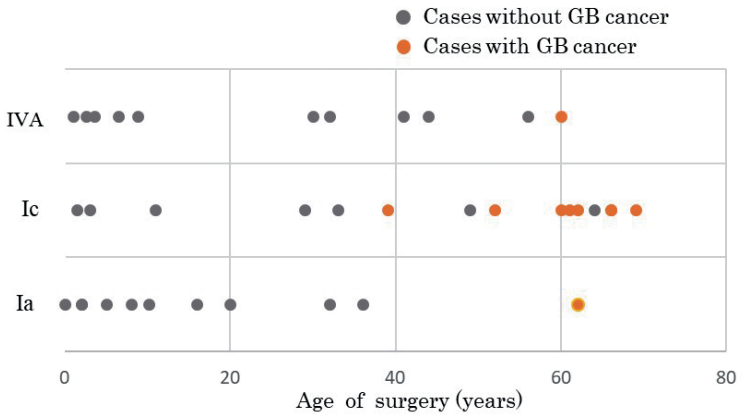

Figure 3. Age distribution of each type in the Todani classification. GB, gallbladder.

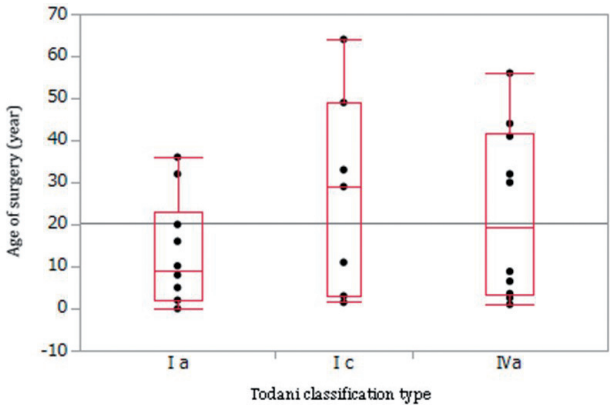

Figure 4. Average surgical age of patients without gallbladder (GB) cancer for all types.

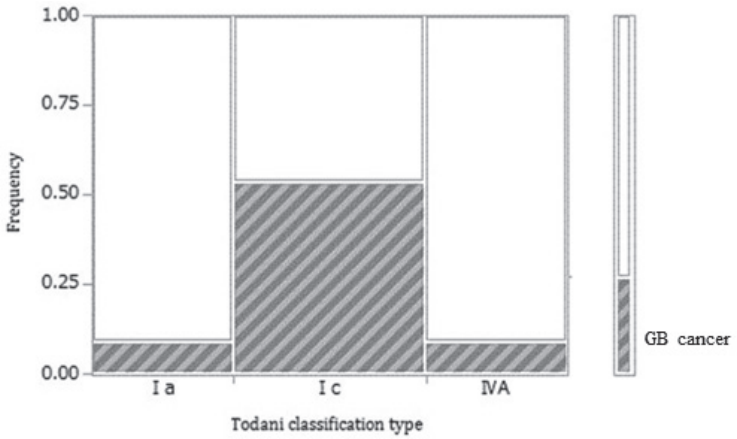

Figure 5. Gallbladder (GB) cancer rate for each type.

Table 3. Comparison of each parameter between patients with and without GB cancer

Variable	GB cancer		p value
	Yes (n=10)	No (n=27)	
Cb (mm^2)	19.12±11.82	1.89±1.61	<0.01
Cp (mm^2)	3.58±1.13	3.23±1.13	0.29
cosθ	0.87±0.15	0.35±0.47	<0.01
MCBD (mm)	20.9±8.70	30.4±18.6	0.32
MCBD/Db	4.48±1.96	25.60±21.09	<0.01
Lc (mm)	20.38±4.04	15.82±6.49	0.15
AMY ($\times 10^5$ U/L)	1.32±1.05	1.81±1.64	0.81

GB, gallbladder; Cb, bile duct cross-sectional area; Cp, pancreatic duct cross-sectional area; θ, junction angle between the pancreatic and bile ducts; MCBD maximum diameter of the congenital biliary dilatation; Lc, length of the common channel; and AMY, amylase.

patients with and without GB cancer, the values were respectively 19.12±11.82 and 1.89±1.61 mm^2 for Cb, 0.87±0.15 and 0.35±0.47 for cosθ, and 4.48±1.96 and 25.60±21.09 for MCBD/Db. These parameters all significantly differed between groups ($p<0.05$). On the other hand, Cp, MCBD, length of the common channel (Lc), and AMY were not significantly different.

Next, we generated scatter diagrams to determine which parameters are associated with the onset age. Figure 6 shows that the Cb of patients with GB cancer was higher than that of patients without GB cancer in all age groups. Figure 7 shows that cosθ had a wide range in the patients without GB cancer, while the values were greater than 0.84 for all patients with GB cancer except one ($\cos\theta=0.5$). This exception was an advanced gallbladder cancer case, which had highly infiltrated the common biliary tract. We suggest that the low value may not reflect the precise junction angle θ before carcinogenesis. Figure 8 shows that MCBD/Db took a wide range of values in the patients without GB cancer, while only low values were observed in patients with GB cancer. A low value indicates that the common bile duct is in a spindle-like or unexpanded form. Table 4 presents the examination result of the correlation with AMY and other parameters. The correlation coefficient between AMY

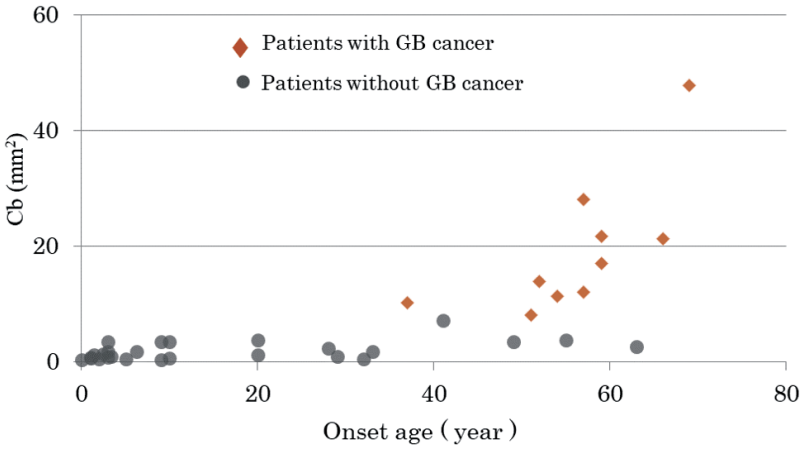

Figure 6. Scatter diagram showing the relationship between junctional bile duct cross-sectional area (Cb) and onset age.

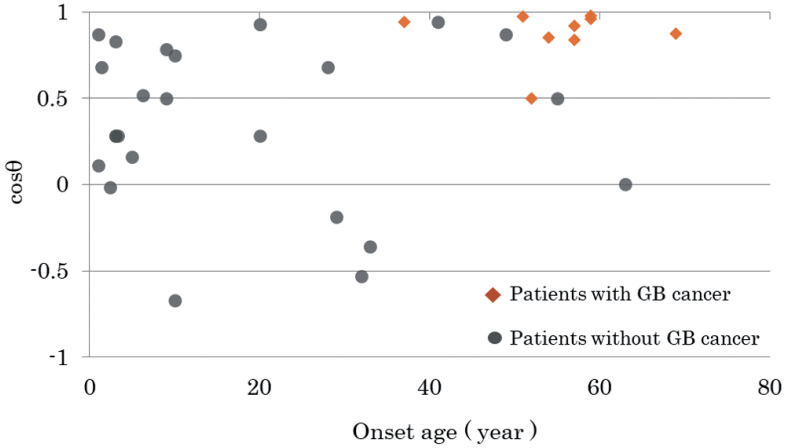

Figure 7. Scatter diagram showing the relationship between cosθ and onset age.

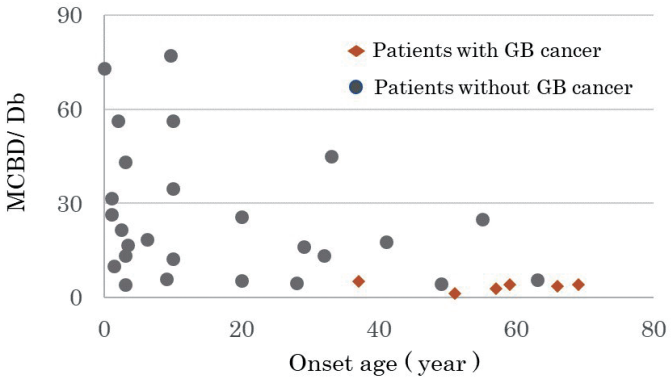

Figure 8. Scatter diagram showing the relationship between the ratio of the maximum diameter of the congenital biliary dilatation to the diameter of the bile duct (MCBD/Db) and onset age.

and cosθ was 0.50 ($p=0.02$), and that between AMY and Lc was 0.47 ($p=0.046$). The other parameters were not correlated with AMY, showing that refluxing pancreatic enzymes were influenced by cosθ and Lc.

Discussion

PBM is a single malformation in which the pancreatic and bile ducts join anatomically outside the duodenal wall, but there are several varieties in terms of their clinical courses and prognosis, owing to differences between the various forms of confluence. Therefore, we chose parameters to quantitatively evaluate these confluence forms, and then evaluated them as carcinogenic predictors.

Patients without GB cancer showed no differences in the surgical age between types (Fig. 4). In addition, the carcinogenic rate clearly differed between each type (Fig. 5). If there had been a type with a low surgical age, curative treatment would be completed before carcinogenesis, so the carcinogenic rate would be expected to decrease. However, since we did not find such a difference in surgical age, it can be inferred that there is a wide range of carcinogenic risk within each type. This means that variations in the connection between bile duct and the pancreatic duct strongly influences GB carcinogenesis.

Next, when comparing each parameter between patients with and without GB cancer, Cb, cosθ and MCBD/Db showed significant differences between patients with and without GB cancer (Table 3). In addition, these parameters behaved differently between patients with and without GB cancer (Figs. 6-8). These findings indicated that these parameters play important roles in carcinogenesis.

Specifically, the Cb of all patients with GB cancer exceeded 8.0 mm^2 (Fig. 6). We believe 8.0 mm^2 is an important boundary value that promotes an increased reflux of pancreatic juices to the biliary tract, and eventually contributes to carcinogenesis.

In addition, most values of cosθ in the patients with GB cancer were greater than 0.84 (Fig. 7), which was correlated with AMY (Table 4). These findings indicate that pancreatic juices may more easily reflux to the biliary tract when the junction angle is smaller, and a value of 0.84 may be an important boundary value that promotes the reflux of pancreatic juices to the biliary tract.

Finally, MCBD/Db reflects the degree of biliary tract dilatation and may be an indicator of the stagnation of bile and refluxed pancreatic juices.

MCBD/Db had values less than 4.3 in all patients with GB cancer, while it ranged widely in the patients without GB cancer MCBD/Db (Fig. 8). This different behavior of MCBD/Db seemed to indicate an important clue of carcinogenesis, and a value of 4.3 may be an important boundary value that controls the reflux of pancreatic juices to the biliary tract.

By examining the parameters listed above, we conclude that cosθ, Cb, and MCBD/Db can be

Table 4. Correlation between AMY and other parameters

Combination of parameters	Correlation coefficient	p value
AMY and Cb	−0.03	0.87
AMY and Cp	0.09	0.69
AMY and cosθ	0.50	0.02
AMY and MCBD	−0.08	0.75
AMY and MCBD/Db	−0.18	0.35
AMY and Lc	0.47	0.046

AMY, amylase; Cb, bile duct cross-sectional area; Cp, pancreatic duct cross-sectional area; θ, junction angle between the pancreatic and bile ducts; MCBD maximum diameter of the congenital biliary dilatation; Db, diameter of the bile duct; and Lc, length of the common channel.

defined as carcinogenic predictors. In addition, from the results of Figures 6-8, the prediction criteria for carcinogenesis are defined as follows.

(1) $\cos\theta \geqq 0.84$

(2) $Cb \geqq 8.0$

(3) $MCBD/Db \leqq 4.3$

While it is impossible to actually evaluate the degree of reciprocal flow of bile and pancreatic juice in vivo, the cutoff values above can be important indicators of the carcinogenic risk of GB cancer in patients with PBM.

Because of the small number of cases, we could not use multiple logistic regression analysis on Cb, $\cos\theta$, and MCBD/Db to determine which is the most useful parameter for carcinogenesis prediction. We therefore plan to accumulate additional cases in the future and evaluate more appropriate carcinogenesis prediction factors.

Acknowledgement

All authors have no COI to declare regarding the present study.

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"Crack and Pave" and Intentional Protrusion of an Endoconduit into the Terminal Aorta for Endovascular Abdominal Aneurysm Repair

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Abstract

An unfavorable iliac artery anatomy is considered a surgical challenge in endovascular aortic repair. The endoconduit technique was performed in an 83 year-old man with abdominal aortic aneurysm with a severely calcified and stenotic iliac artery. The calcified iliac artery was "cracked" before paving it with an 8 mm covered stent. The proximal 2 cm of the endoconduit was intentionally protruded into the terminal aorta, which was used for the distal landing of the contralateral limb of a bifurcated stent graft. These technical modifications such as cracking before paving and protrusion were successfully applied to this patient.

Key Words: Endoconduit; Abdominal aortic aneurysm; Endovascular aortic repair

Introduction

The endoconduit technique is one of the alternative techniques used for a narrow and calcified iliofemoral access route in endovascular aortic repair (EVAR). Here, we present a case of abdominal aortic aneurysm (AAA) with an unfavorable iliac access for EVAR that was treated using the Viabahn endoprosthesis (W. L. Gore & Associates, Newark, Delaware, USA) as an iliac endoconduit, which was intentionally protruded into the terminal aorta.

Case Report

The report describes the case of an 83 year-old man with rapidly expanding AAA who was recommended EVAR. He had a treatment history of right aortofemoral artery bypass and left femoropopliteal artery bypass.

Computed tomography (CT) angiography revealed a 4.7 cm AAA and an adequate proximal sealing zone. The left common iliac artery (CIA) and external iliac artery (EIA) were narrowed with heavy calcification throughout their length, with the smallest diameter being 4.0 mm. The left internal iliac artery (IIA) and right EIA were occluded, with the patent right aortofemoral artery bypass. Thus, the

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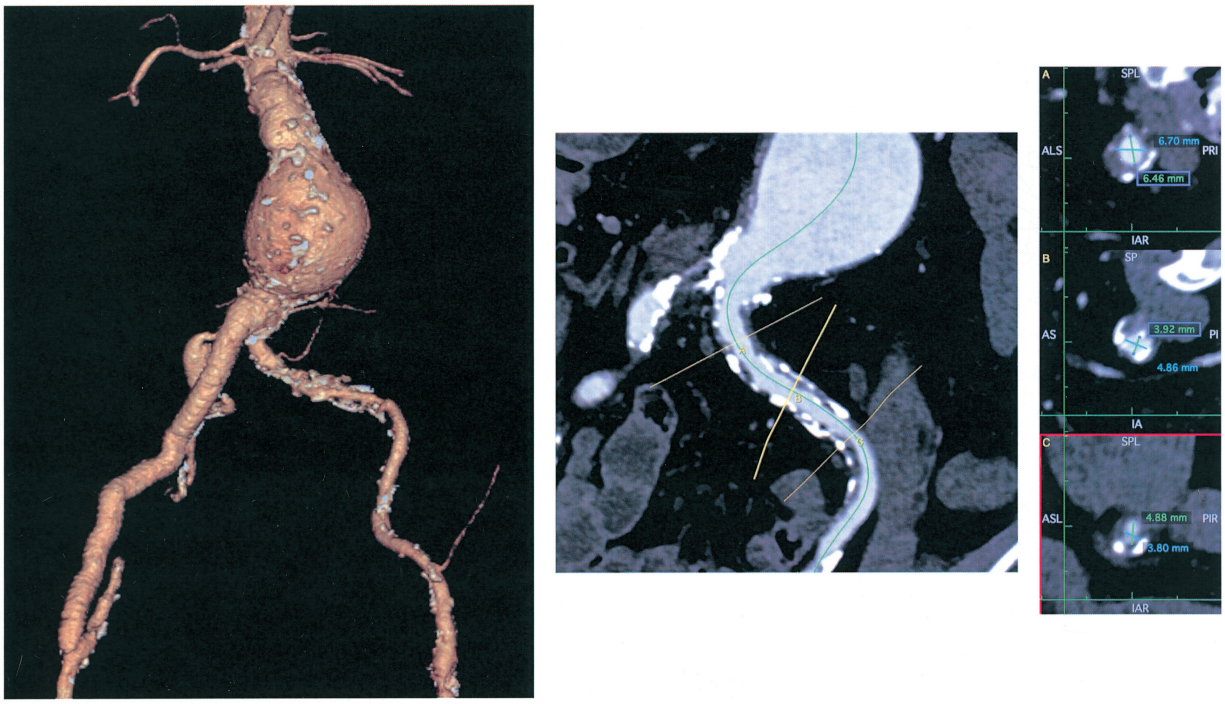

Figure 1. Left figure; Preoperative reconstruction of computed tomography angiogram revealed the infrarenal abdominal aneurysm and aortofemoral bypass. Right two figures; The multi-planar reconstruction computed tomography showed the left iliac artery was narrowed with heavy calcification throughout its length.

patient was diagnosed with a rapidly expanding AAA and was recommended EVAR.

The operation involved creation of bilateral inguinal incisions under general anesthesia to expose the left common femoral artery (CFA) and a prosthetic graft in the right groin. A sheath was placed into each incision. Next, the right IIA was coil embolized with a 10 mm×40 cm 3D Interlock-35 Fibered coil (Boston Scientific, Natick, MA) and 6 mm Tornado Embolization Coils (Cook Medical Inc, Bloomington, Ind, US) through the left CFA access. After embolization, the left iliac artery was predilated with an 8 mm semi-compliant balloon catheter (Wanda, Boston Scientific, Natick, MA, USA), which led to the intentional rupture of the iliac artery. Then, a 8×100 mm Viabahn endoprosthesis (JHJR081002J; W. L. Gore & Associates, Newark, Delaware, USA) was deployed. The proximal 2 cm of this device was intentionally protruded from the common iliac artery to the terminal aorta. Thereafter, we aggressively performed balloon dilatation using the same balloon catheter. Vigorous high-pressure dilatation at the origin of the left CIA was carefully avoided because rupture of this site would have been difficult to treat. During this procedure, the hemodynamics of the patient remained stable. Thereafter, a 23×12×140 mm main body of the Excluder (RLT231214J; W.L. Gore & Associates) was deployed through the right prosthetic graft, and the contra-gate was cannulated. A 16×10×70 mm iliac extension (PLL161007J; W.L. Gore & Associates) was selected as the contralateral leg and was deployed inside the protruded portion of the Viabahn endoprosthesis device. A 23×23×30 mm aortic cuff (PLA230300J; W.L. Gore & Associates) was added to treat a type 1a endoleak. There was no type 1b or type 3 endoleak observed. The patient made an uncomplicated recovery. Postoperative CT angiography confirmed complete exclusion of the aneurysm sac and no stenosis on the overlapping stent grafts.

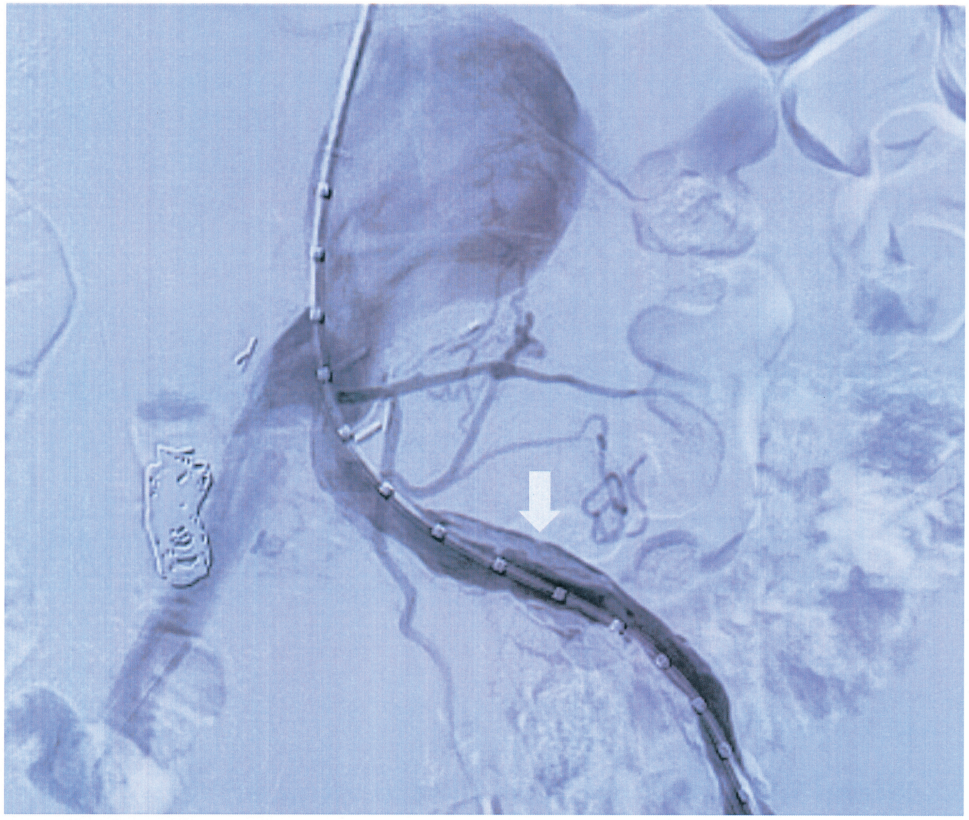

Figure 2. Intraoperative arteriogram after "cracking" the left iliac artery showed a sealed rupture.

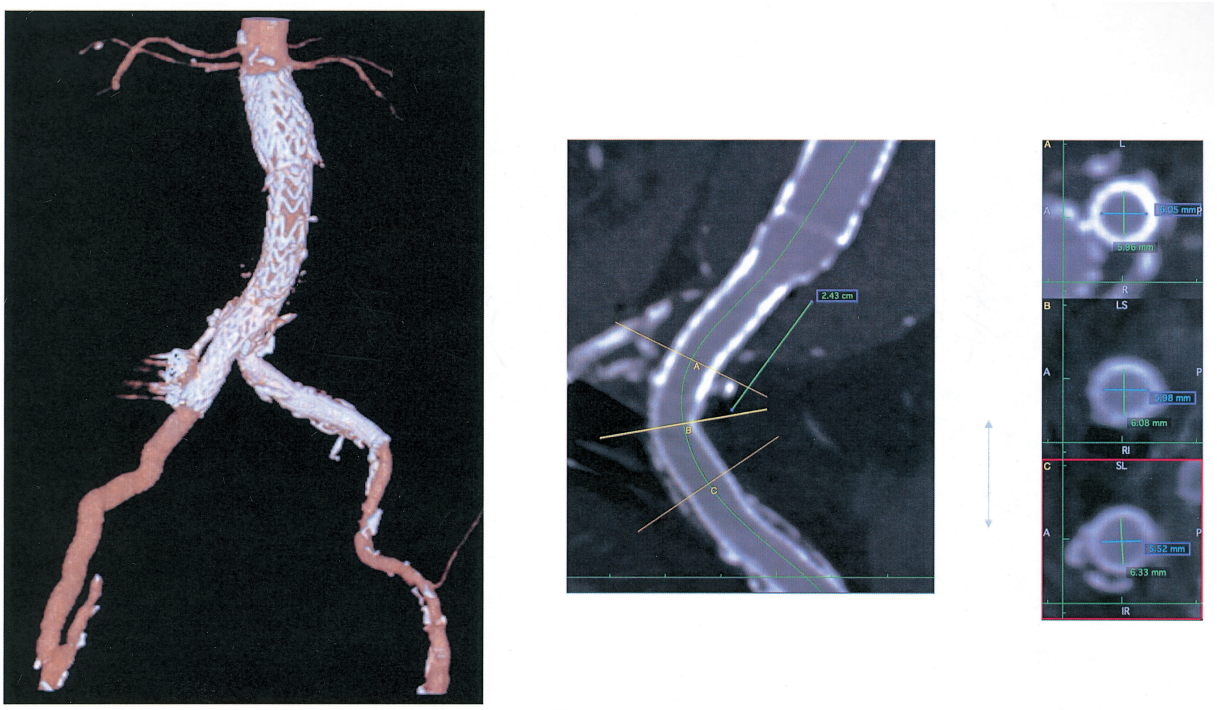

Figure 3. Left figure; Postoperative reconstruction of computed tomography angiogram revealed no endoleak and patency of the endoconduit. Right two figures; Sagittal section of computed tomography angiogram showed the most proximal part of the endconduit was protruded about 2 cm into the aorta. There wass no stenosis in the overlapped endoconduit.

Discussion

Despite the recent development of low-profile devices that range from 6.1 to 7.5 mm in diameter, it is extremely challenging to access severely calcified and advanced atherosclerotic iliac arteries. The most common solutions to access such arteries are aortouniiliac grafting and cross-femoral bypass when a unilateral iliac artery is suitable for the access[1] and open iliac conduits[2]. Although both procedures are reliable, compared with the standard femoral approach, higher morbidity has been reported for the aforementioned techniques[1,2].

In various fields, the endoconduit technique has been reported to be a useful alternative access when high-profile device passage is required[3,4]. This technique entails the deployment of a covered stent in the unfavorable iliac arteries with dilation up to large diameters with a balloon catheter to cause controlled rupture. Compared with the retroperitoneal open iliac conduit technique, the endoconduit technique has been reported to be a more reliable and safer approach because of the lower incidence of iliofemoral complications[5]. The midterm primary-assisted patency of an endoconduit has also been reported to be high[6].

Covered stents with a diameter of ≧10 mm have been used most often as endoconduits in the past[6]. Recently, the development of low-profile devices has enabled the use of an endoconduit measuring 8 mm in diameter for EVAR. In our case, the right CIA was narrow and continuously calcified. Performing conventional EVAR could cause stent graft infold even if we use the minimum diameter leg. Therefore, we considered an 8 mm Viabahn as an endoconduit was the best fit to the distal landing to the 7 mm EIA.

The drawbacks of an oversized endoconduit include injury at the entry site of the CFA, injury to the iliac artery by the distal edge of the endoconduit, and infolding[3,7]. Therefore, the use of endoconduits of a smaller size may reduce the incidence of these complications.

In the present case, we were concerned that complete rupture of the calcified iliac artery may not be achieved with the 8 mm dilation with a balloon catheter after the deployment of the 8 mm Viabahn, resulting in recoiling and persistent stenosis. Therefore, we performed dilatation before endoconduit deployment to confirm reliable cracking, although this carried the risk of free rupture and hemodynamic instability. If iliac rupture was not achieved, a larger balloon and non-compliant balloon catheter were ready for use. In the most proximal part of the CIA, only mild predilatation was performed because rupture of this area could not have been easily treated; however, mild stenosis of this lesion was acceptable. We planned to deploy the endoconduit in such a way that the most proximal part was protruded 2 cm into the aorta to overlap the each stent graft. This allowed complete opening of an 8 mm caliber lumen and performing a drastic balloon expansion in this area. As a result, the iliac extender with a distal diameter of 10 mm could fit the completely dilated Viabahn, even with the possibility of residual stenosis at the origin of the left CIA.

Acknowledgements

All authors have no conflicts of interest to declare regarding the present case report.

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