Chronic atrophic gastritis is a progressive disease: analysis of medical reports from Shanghai (1985–2009)

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INTRODUCTION We aimed to examine the turnover of chronic atrophic gastritis (CAG) pathologically and endoscopically and explore its potential causes.
METHODS A retrospective analysis was conducted of prospective data collected from 1,592 patients who underwent gastroscopy three times or more during the period 1985–2009 at Renji Hospital, Shanghai, China. Pathological and endoscopic findings were analysed. Data collected included gender, age, length of follow-up period, family history, past medical history, history of _Helicobacter (H.) pylori_ infection, drug history for the use of proton pump inhibitors (PPIs), antacids and non-steroidal anti-inflammatory drugs [NSAIDs], and lifestyle history, including the patients' eating habits.
RESULTS 23 (1.44%) patients presented with gastric cancers resulting from CAG and 349 (21.92%) patients had dysplasia. Pathological and endoscopic findings suggested that the proportion of patients with worsening gastric mucosa during the atrophic and intestinal metaplasia (IM) phases was over 35% with increasing age. Gastric mucosa was found to be pathologically aggravated by carbonated drinks and fast food, and pathologically degenerated by _H. pylori_ infection. Smoking deteriorated the gastric mucosa. Side dishes of vegetables may benefit the gastric mucosa even in the atrophic and IM phases.
CONCLUSION Our findings support the consensus that CAG is a progressive disease. Potential factors that were found to affect the state of the gastric mucosa in our patient group were gender, _H. pylori_ infection, use of PPIs or NSAIDs, and intake of vegetable side dishes, spicy food, carbonated drinks and fast food.

INTRODUCTION

Chronic atrophic gastritis (CAG) is one of the most common diseases in China. It is also an established precursor of intestinal-type gastric cancer (GC),[1-5] which is the third most common cause of cancer-related death in China.[6] Although the incidence and mortality of GC declined slightly between 2000 and 2005, this trend was attributed entirely to male awareness of the disease, with the incidence and mortality rates in female patients showing a slight increase for the same period.[6] Correa et al have suggested that in gastric carcinogenesis, a cascade of precursor lesions such as chronic gastritis, glandular atrophy, intestinal metaplasia (IM) and dysplasia presents itself prior to the development of gastric adenocarcinoma.[7,8] According to Kuipers, a majority of patients with _Helicobacter_ (H.) _pylori_ infection exhibit chronic superficial gastritis without any clinical symptoms, and only a small proportion of infected individuals develop CAG and GC.[9] Such clinical diversity in patients with CAG is assumed to be caused by the interplay of environmental factors, differences in host susceptibility and the pathogenicity of various _H. pylori_ strains[10,11] as well as dietary factors, among others.

Epidemiological studies from Japan, China, Tanzania, the Dominican Republic, the Netherlands and Mozambique[12-16] have suggested an inadequate association between CAG and GC.

The pathological[17,18] and endoscopic[19] findings of the gastric mucosa in patients with CAG were examined and the patients surveyed for other factors such as family history, past medical history, history of _H. pylori_ infection,[20-22] drug history,[23-26] lifestyle history and the patients' eating habits for any correlation with prognosis. The proportion of patients with CAG that pathologically worsened was, however, not clear, and it was assumed that several factors, including gender, age, family history, the relationship between _H. pylori_ infection and pathological diagnosis, drug history and lifestyle might have a role to play in CAG prognosis. Findings were explored to determine the characteristics of CAG in the clinical phase as well as the factors that caused an improvement or worsening in the condition of the gastric mucosa.

METHODS

Patients enrolled in the study comprised outpatients being treated for CAG at the Department of Gastroenterology, Renji Hospital, Shanghai, China, who underwent gastroscopy three times or more and were referred between 1985 and 2009 by a physician at the hospital. Patients with non-atrophic gastritis and a pathological diagnosis of GC at the first endoscopic examination were excluded from the study. The Ethics

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Committee of Shanghai Jiao-Tong University School of Medicine, to which the Renji Hospital is affiliated, approved the protocol. Research was carried out according to the provisions of the Helsinki Declaration of 1975.[27] Endoscopic examinations were performed for patients with a risk of early GC, where the patient's discomfort remained after taking medicine for more than six months or when there was a need for follow-up.

Referred patients were required to have routine check-ups of blood pressure, electrocardiogram, liver function test and hepatitis B surface antigen, and to fast for at least six hours before the examination. All parts of the upper gastrointestinal (GI) tract were carefully examined for any GI lesions. At least two biopsies were taken from the antral part during the patient's first gastroscopic examination. Patients on follow-up, especially those with dysplasia, were required to have 2–5 annual biopsies to track their mucosal condition compared to that at their previous appointment. Patients with predisposing factors such as strong family history, *H. pylori* infections, drug history and living habits were also followed up by telephone.

H. pylori infection was detected using the *H. pylori* rapid urease test during endoscopy examinations and Giemsa staining of pathological specimens. The test for *H. pylori* infection was assumed to be positive if both results were positive. However, if only one examination yielded positive results, the patient was required to take a confirmatory 13C urea breath test, especially when negative results were obtained for the *H. pylori* rapid urease test but the Giemsa-stained pathological specimens were positive. The 13C urea breath test was used as a confirmatory test, as it is considered the gold standard for *H. pylori* detection[2,21,22] and also to avoid the influence of drugs such as proton pump inhibitors (PPIs) and H2 receptor antagonists. *H. pylori* infection was taken to be absent if the two tests during endoscopy yielded negative results. The 13C urea breath test was also performed following treatment for patients initially positive for *H. pylori* infection in order to confirm complete eradication of the pathogen.

Biopsy specimens were examined by experienced pathologists from the Department of Pathology at Renji Hospital who had at least eight years of relevant experience. For patients with suspected malignancies of the upper GI tract, the pathologists confirmed the final diagnoses before and after surgery. The updated Sydney System score[28] was used as a diagnostic criterion irrespective of pathological and endoscopic findings. To differentiate the pathological condition as positive development, no change or negative development, a marking scheme was introduced based on the following equation:

$$\frac{(S1 \times B2) + (S2 \times B2) + \ldots + (Sn \times Bn)}{Bn}$$

where 'S' was the severity of the particular biopsy tissue, 'B' the relative biopsy tissue, '1' the first biopsy tissue, '2' the second biopsy tissue and 'n' the quantity of all biopsy tissues. Subsequent to calculation, scores were obtained for the first and second
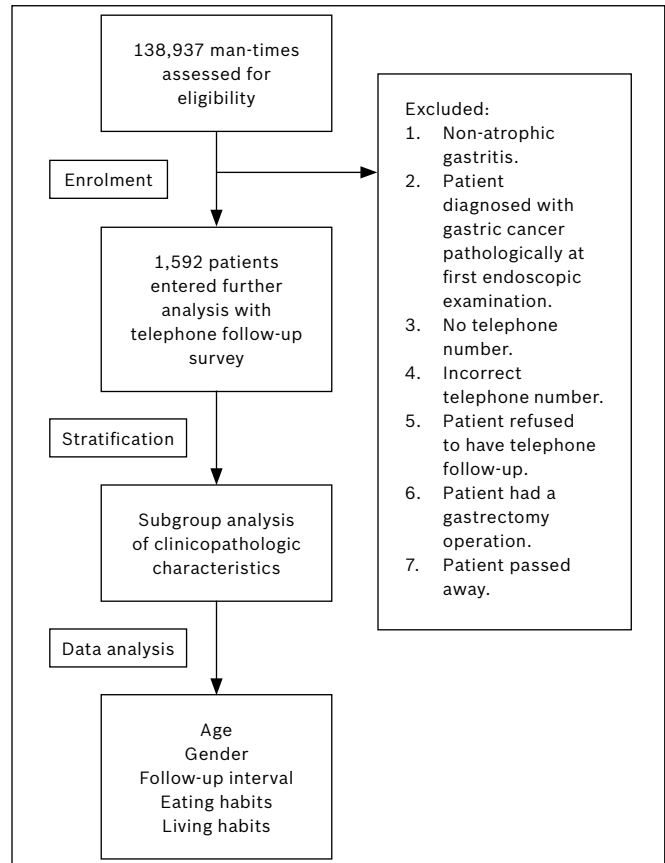

Fig. 1 Flow diagram shows the various stages of the study.

follow-up visits. A lower second score implied an improvement in the condition of the patient's gastric mucosa. There was no change in the patient's gastric mucosa if the two scores were the same.

A questionnaire was distributed to obtain detailed information on family history, past medical history, history of *H. pylori* infection, drug history, lifestyle and eating habits. The questionnaire was administered by six teachers at the Shanghai Institute of Digestive Disease, who were systematically trained to be polite and compassionate to the patients and to avoid calling patients at busy hours or during work. A database (Microsoft Excel 2007, Microsoft Corp, Redmond, WA, USA) was constructed once the questionnaires were collected. Pathological and gastroscopic reports were obtained from the database at Renji Hospital and analysed accordingly. Fig. 1 visualises the various stages of this retrospective study. All patients were required to comply with our treatment regime and be followed up regularly. The patients were asked whether they had understood the study and were requested to cooperate and provide pertinent information truthfully. The exact follow-up duration was based on each patient's signs and symptoms.

Patients were categorised based on age into the following age groups: ≤ 44 years; 45–54 years; 55–64 years; and ≥ 65 years. Categorical data were compared using the chi-square test, and logistic regression analysis was performed, where appropriate. All statistical calculations were performed using the SAS statistical software version 8.02 (SAS Institute Inc, Cary, NC, USA). A two-tailed $p < 0.05$ was considered statistically significant.

Table I. Findings of the telephone survey of study participants (n = 1,592).

Variable	Inflammation			Atrophy			Intestinal metaplasia			Endoscopy		
	B	N	W	B	N	W	B	N	W	B	N	W
Gender												
Men	302	409	155	286	251	291	261	188	237	178	475	214
Women	249	356	121	230	229	230	216	149	190	157	390	179
History of *H. pylori* infection												
H. pylori (–)	341	499	168	319	320	314	317	209	255	202	558	249
H. pylori (||)	165	204	71	148	124	152	122	98	130	93	236	111
H. pylori (±)	18	12	11	15	6	19	7	5	19	11	18	12
H. pylori (+)	27	50	26	34	30	36	31	25	23	29	53	21
Follow-up period (yr)*												
≤ 1	489	420	333	468	273	383	409	182	354	291	468	231
1–2	1,659	1,898	1,045	1,616	1,127	1,487	1,347	814	1,308	962	1,543	902
3–7	766	741	534	694	445	684	513	289	585	373	522	349
≥ 8	106	122	150	127	68	140	88	48	120	20	39	21
History of PPI use												
Not in use	312	421	156	288	276	291	276	200	235	183	476	230
In use	239	344	120	228	204	230	201	137	192	152	389	163
Eating habits												
Vegetable side dishes	219	297	105	195	210	190	199	136	164	120	340	161
Meat side dishes	43	81	29	52	42	50	42	28	42	41	82	30
Balanced	289	387	142	269	228	281	236	173	221	174	443	202
Intake of spicy foods												
Less (≤ 6 meals/wk)	377	564	192	372	341	365	341	250	317	236	613	285
Often (≥ 7 meals/wk)	174	201	84	144	139	156	136	87	110	99	252	108
Intake of carbonated drinks												
Less (≤ 3 L/wk)	482	668	239	453	421	454	426	295	374	292	756	342
Often (> 3 L/wk)	69	97	37	63	59	67	51	42	53	43	109	51
Intake of fast foods												
Less (≤ 6 meals/wk)	472	667	250	439	419	468	417	301	383	293	756	341
Often (≥ 7 meals/wk)	79	98	26	77	61	53	60	36	44	42	109	52
Family history												
No	384	577	191	373	348	369	351	245	287	245	615	292
Yes	167	188	85	143	132	152	126	92	140	90	250	101
Past history												
No	540	741	270	501	469	509	459	331	415	324	845	383
Yes	11	24	6	15	11	12	18	6	12	11	20	10
Smoking												
No	466	648	245	449	401	448	410	287	366	285	740	335
Yes	85	117	31	67	79	73	67	50	61	50	125	58
Alcohol consumption												
No	507	711	262	486	438	487	440	313	408	305	809	367
Yes	44	54	14	30	42	34	37	24	19	30	56	26

* All biopsies taken during examination were compared.
B: gastric mucosa is getting better; N: gastric mucosa shows no changes; W: gastric mucosa is getting worse; *H. pylori* (–): gastric mucosa is not infected by *H. pylori*; *H. pylori* (\|\|): gastric mucosa was infected with *H. pylori* but treated successfully; *H. pylori* (±): chronic infection of gastric mucosa by *H. pylori*; *H. pylori* (+): gastric mucosa is infected by *H. pylori*; PPI: proton pump inhibitors

RESULTS

From a total of 138,937 man-times spent during the years 1985–2009, 1,592 patients or 9,583 (6.89%) man-times were eligible for the study. The average number of examinations per patient was 6.02 times. 47 (2.95%) patients were diagnosed with GCs, with 23 (1.44%) patients developing GC from CAG and 24 (1.51%) patients from ulcers pathologically. 349 (21.92%) patients had dysplasia; 579 biopsies (n = 273) showed mild dysplasia, 116 biopsies (n = 69) showed moderate dysplasia and ten biopsies (n = 7) indicated severe dysplasia. The seven patients who had severe dysplasia progressed to GC and subsequently underwent gastrectomies at our hospital.

Logistic regression analysis showed that during the inflammatory phase, the condition of the gastric mucosa in women displayed positive improvements more often than men (p < 0.01). Patient turnover was related to follow-up intervals, i.e. the condition of the gastric mucosa was worse with longer intervals (p < 0.01). As the available data produced unsatisfactory results, a further survey was planned for these patients via telephone follow-ups to determine the factors that contributed to the changing condition of the gastric mucosa. Table I details the findings of the telephone survey of 1,592 patients.

Endoscopic and pathological findings supported the assumption that CAG was a progressive disease. Age and follow-

Table II. Correlation between age and findings of study participants (n = 1,592).

Variable	Inflammation				Atrophy				Intestinal metaplasia				Endoscopy			
	B	N	W	p-value	B	N	W	p-value	B	N	W	p-value	B	N	W	p-value
Age ≤ 44 yrs																
Intake of spicy foods																
Less (≤ 6 meals/wk)	68	120	41	< 0.01												
Often (≥ 7 meals/wk)	71	63	34													
Age 45–54 yrs																
History of *H. pylori* infection																
H. pylori (−)	133	186	50	0.02					118	87	83	< 0.01				
H. pylori (||)	61	77	20						43	36	48					
H. pylori (±)	-	-	-						1	0	9					
H. pylori (+)	19	22	17						11	12	12					
Gender																
Male					56	84	62	0.068					48	112	53	< 0.05
Female					124	116	121						83	201	88	
Age 55–64 yrs																
Eating habits																
Balanced					61	42	74	< 0.05	57	43	61	0.088				
Vegetable side dishes					51	62	48		64	36	42					
Meat side dishes					12	9	14		10	5	17					
Gender																
Male	66	95	26	0.076									40	106	41	< 0.05
Female	56	100	44										30	103	67	

B: gastric mucosa is getting better; N: gastric mucosa shows no changes; W: gastric mucosa is getting worse; *H. pylori* (−): gastric mucosa is not infected by *H. pylori*; *H. pylori* (||): gastric mucosa was infected with *H. pylori* but treated successfully; *H. pylori* (±): chronic infection of gastric mucosa by *H. pylori*; *H. pylori* (+): gastric mucosa is infected by *H. pylori*

up interval were significant factors. The condition of the gastric mucosa was worse in older patients if no intervention was performed. Endoscopic findings revealed that increasing age was linked to worsening of the gastric mucosa. Younger patients had more positive developments than older ones. The follow-up interval played a vital role in the prognosis of the gastric mucosa, with shorter intervals (that is, more frequent follow-up) being associated with a better prognosis. Endoscopically, the condition of the gastric mucosa was worse in patients who smoked at least 20 cigarettes a day for at least five years. From a pathological point of view (inflammatory, atrophic and IM stages), the condition of the gastric mucosa worsened in more men than women (Table I). A poorer condition in the inflammatory phase was always associated with IM. Smoking worsened the condition of the gastric mucosa in the inflammatory phase.

The findings of the survey were analysed for age-related correlations (Table II). Patients in the age group ≤ 44 years in the inflammatory phase improved with regular intake of spicy food (p < 0.01). In patients aged 45–54 years, endoscopic findings for men were worse than those for women (p < 0.05). However, in the atrophic phase, the reverse was true, with the gastric mucosae of men showing greater improvement compared to those of women (p = 0.068). Inflammatory worsening of the gastric mucosa was strongly related to *H. pylori* infection (p < 0.05). The condition of the gastric mucosa in IM patients with chronic and continuously positive *H. pylori* infection worsened (p < 0.01), underscoring the importance of early eradication of *H. pylori* before the condition of the gastric mucosa worsens. In the age group 55–64 years, the findings for men were worse than those for women on endoscopy and in the atrophic stage (p < 0.05), but the gender difference was

not significant in the inflammatory phase (p = 0.076). Intake of vegetable side dishes was beneficial in the atrophic stage (p < 0.05) but not the IM stage (p = 0.088).

Table III examines the relationship between the intake of carbonated drinks and fast food and the prognosis of CAG, as many young patients with CAG in the atrophic stage were found to present at the hospital frequently. This suggested that the intake of carbonated drinks and fast food may be a significant factor in CAG prognosis and that the effects may be worse for older patients.

DISCUSSION

Atrophy of the gastric mucosa, a common pathological process due to a thinning of the gastric mucosa,[28] has been defined as a loss of glands,[29] and is categorised as either metaplastic or non-metaplastic atrophy. In metaplastic gastric mucosal atrophy, normal (native) glands are replaced by metaplastic glands, i.e. glands that do not normally belong to the area, or pseudopyloric glands. Non-metaplastic gastric mucosal atrophy is characterised by a loss of appropriate glands and is accompanied by fibrosis or fibromuscular or inflammatory cells proliferating in the lamina propria.[30-32] Atrophy is a strong indicator of IM and has generally been regarded as a condition that predisposes to malignancy. For this reason, a better understanding of the sequence of events in gastric carcinogenesis will allow physicians to better identify patients at risk and to implement better management strategies.[33-35] Given that atrophy in the gastric mucosa may require a long time to recover and that atrophy and IM may be progressive, reversing the condition of the gastric mucosa may become very difficult once CAG reaches the 'point of no

Table III. Age-dependent correlation between CAG prognosis and the intake of carbonated drinks and fast foods.

Variable	Inflammation			Atrophy			Intestinal metaplasia			Endoscopy		
	B	N	W	B	N	W	B	N	W	B	N	W
Intake of carbonated drinks												
Age ≤ 44 yrs												
Less (≤ 3 L/wk)	114	144	58	98	94	100	78	58	72	68	178	70
Often (> 3 L/wk)	25	39	17	23	21	27	17	12	18	16	42	23
Age 45–54 yrs												
Less (≤ 3 L/wk)	185	250	74	160	171	158	153	113	137	117	267	125
Often (> 3 L/wk)	28	35	13	20	29	25	20	22	15	14	46	16
Age 55–64 yrs												
Less (≤ 3 L/wk)	111	177	66	110	106	125	123	78	104	61	194	99
Often (> 3 L/wk)	11	18	4	14	7	11	8	6	16	9	15	9
Age ≥ 65 yrs												
Less (≤ 3 L/wk)	72	97	41	85	50	71	72	46	61	46	117	48
Often (> 3 L/wk)	5	5	3	6	2	4	6	2	4	4	6	3
Intake of fast food												
Age ≤ 44 yrs												
Less (≤ 6 meals/wk)	108	138	62	91	86	107	79	52	74	63	178	67
Often (≥ 7 meals/wk)	31	45	13	30	29	20	16	18	16	21	42	26
Age 45–54 yrs												
Less (≤ 6 meals/wk)	182	256	82	154	179	166	148	123	139	121	270	129
Often (≥ 7 meals/wk)	31	29	5	26	21	17	25	12	13	10	43	12
Age 55–64 yrs												
Less (≤ 6 meals/wk)	110	182	66	113	106	126	120	79	111	64	195	99
Often (≥ 7 meals/wk)	12	13	4	11	7	10	11	5	9	6	14	9
Age ≥ 65 yrs												
Less (≤ 6 meals/wk)	72	91	40	81	48	69	70	47	59	45	113	46
Often (≥ 7 meals/wk)	5	11	4	10	4	6	8	1	6	5	10	5

return'.[2,36-39] Although it is possible that we may have missed CAG locally during the initial endoscopic investigations, it is also likely that the large number of biopsies taken and the lengthy follow-up period enforced would have helped to overcome any bias present.

We found that CAG, a progressive disease, is closely related to older age. Our results also suggested that an extended period of follow-up was essential, as the condition of the gastric mucosa declined in at least 30% of patients, especially in elderly patients. 47 (13.47%) out of 349 patients who had dysplasia progressed to GC, of which 23 (6.59%) patients progressed pathologically from CAG and 24 (6.88%) from ulcers. For the remaining 302 (86.49%) patients with dysplasia, interventions were performed within a year of the diagnosis of dysplasia before the gastric mucosa could progress to GC. This finding highlights the importance of early identification and prevention in the case of patients with CAG. While 23 (6.59%) patients with CAG progressed to dysplasia and GC at our centre, de Vries et al,[14] in their study, recommended a 1% cancer rate in their study population. The higher incidence seen in our study may have been caused by the longer follow-up periods in this study and the high infection rate of *H. pylori* in China. In the inflammatory and atrophic phases, the gastric mucosae in men showed slower recovery than in women. This difference may in part be due to lifestyle habits, including excessive smoking and drinking among men. It may also be related to work-associated stress.

Although family history may be a significant factor in GC and the precancerous stage of the disease, it is not associated with the severity and turnover of the gastric mucosa. Other factors affecting the turnover and severity of atrophy of the gastric mucosa were *H. pylori* infection, eating habits, lifestyle and the inclusion of fresh fruits and vegetables in the diet. Indeed, capsaicin in spicy food has been shown to increase blood flow to the gastric mucosa,[40,41] and therefore may help to slow down *H. pylori* infection. While we did find that worsening inflammation of the gastric mucosa always reflected infection of the gastric mucosa by *H. pylori*, it should be noted that the eradication of *H. pylori* infection may not prevent GC. Our results indicated that the eradication of *H. pylori* infection may aid in improving the condition of the gastric mucosa in the inflammatory and atrophic phases, but not in the IM phase or for patients with dysplasia. Younger patients[42,43] (age ≤ 44 years) who regularly consumed carbonated drinks and fast food saw more damage to the gastric mucosa irrespective of whether they were in the inflammatory, atrophic or IM phases. In patients aged 45–54 years, a pathological worsening of the condition of the gastric mucosa was seen in those who regularly consumed fast food.

Although some studies[44-48] on the association between the use of aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs) and GC have suggested that regular intake of aspirin may prevent GC, our results were to the contrary, as we found that the use of NSAIDs may exaggerate the inflammation endoscopically and pathologically. NSAIDs may cause atrophy to intensify if patients use them in the long term. Although our data did not demonstrate a deterioration of the gastric mucosa in the atrophic and IM

phases with the intermittent use of PPIs, this possibility could not be ruled out either.

The annual incidence of cancer from CAG has been reported to be 0.5%–1%.[14] Therefore, it is imperative that early, more economical and convenient methods for the diagnoses of GC be introduced for at-risk patients. We recommend that patients without IM or dysplasia undergo routine checkups with endoscopies every 1–2 years, and those with moderate-to-severe atrophy associated with IM should have routine annual checkups. Patients with mild dysplasia should be followed up every 6–12 months, and endoscopy and pathology reviews repeated for patients with severe dysplasia. For biopsies of patients with dysplasia, endoscopists must rule out that the biopsy specimens were not taken from a cancerous tissue or lesion, and treatment with endoscopy or gastrectomy should be used when necessary.[14,15]

This study was not without limitations. Variables such as a high-salt or high-sugar diet, intake of green tea or coffee were not included in the study, as these would have further complicated the measurements and caused difficulties during follow-ups. Our findings were also not conclusive regarding the effect of the regular use of aspirin or non-aspirin NSAIDs and a possible reduction in the risk of developing GC, the role of PPI usage and a linked deterioration of the gastric mucosa in the atrophic and IM phases, the relevance of the intake of carbonated drinks and fast food in younger patients with or without precancerous lesions.

In conclusion, larger studies are warranted to determine the role of CAG in GC and the correlation between CAG and a more complete range of lifestyle variables and factors that may cause the gastric mucosa to deteriorate. We suggest that studies involving a larger group of centres be conducted and more precise equipment be developed. These will help to perfect future clinical trials as well as provide relevant information to clinicians.

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