Lymphology 45 (2012) 165-176

NATURAL HISTORY OF LYMPH PUMPING PRESSURE AFTER PELVIC LYMPHADENECTOMY

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ABSTRACT

Lower limb lymphedema is difficult to prevent and diagnose early because its natural history is unclear. Therefore, the aim of this study was to clarify its pathogenesis and to identify risk factors that may lead to early diagnosis. In 29 patients, aged 25 to 74 years with cervical, uterine, or ovarian cancer who underwent pelvic lymphadenectomy, indocyanine green fluorescence lymphangiography was performed with an infrared camera system, and lymph pumping pressure was measured indirectly preoperatively, and one, two, three, and six months postoperatively. Of these 29 patients, 22 (75.9%) completed the examinations. In the non-lymphedema group, the average lymph pumping pressure did not change significantly at postoperative follow-up compared with preoperative values. On the other hand, lymph pumping pressure increased at various time points in five patients who developed early lymphatic changes with dermal diffusion at the level of the proximal femur. An increase in lymph flow path resistance due to pelvic lymphadenectomy resulted in an initial increase in lymph pumping pressure, followed by a subsequent decrease, in the early lymphatic changes group. This trend in the pressure change signifies that the lymph vessels became dysfunctional as they were overwhelmed by the overload condition and this feature may be a clinically useful signal for the early diagnosis of developing lymphedema.

Keywords: gynecological cancer, lower limb lymphedema, natural history, indocyanine green (ICG) fluorescence lymphangiography, lymph pumping pressure

Lower limb lymphedema, which develops in 20% to 30% of patients following gynecological surgery with lymphadenectomy (1,2), is one of the disabling complications that have a significant impact on patients' activities of daily living and quality of life. Prevention, early diagnosis, and treatment before progression to a severe condition will benefit patients. However, it is very difficult to predict which patient will develop lymphedema (3-9), because its occurrence, onset time, and severity vary widely in each patient after the same surgical procedure.

Lymphedema is caused by impaired lymphatic flow return. Its detailed pathogenesis has been studied with fluorescence imaging of lymph vessels using indocyanine green (ICG) dye and near-infrared cameras, called fluorescence lymphangiography (10-18). These devices can visualize clear images of lymphatic dynamics in real time with a short inspection time compared with conventional lymphoscintigraphy. In the early stage of lymphedema, lymph flow stasis and reflux in the skin, which are collectively called dermal diffusion, at the level of the proximal femur and lower abdomen have been reported as a characteristic pattern seen with fluorescence imaging (15-17,19).

On the other hand, it has been reported that the indirect lymph pumping pressure measured with lymphoscintigraphy or fluorescence lymphangiography in combination with a sphygmomanometer was lower in patients with chronic lymphedema than in healthy volunteers (18,20,21). Human studies have revealed that the contractile function of lymph vessels increase initially, corresponding to an increase in lymph flow path resistance in the proximal lymph vessels, but if the overloaded condition continues, the lymph vessel contractility decreases progressively (22-24). These findings suggest that the lymphatic dysfunction might be related to the onset of lymphedema. However, no previous clinical studies have evaluated the dynamic changes of lymph pumping pressure in cancer patients over time. The purpose of the present research was to assess lymphatic function using lymph pumping pressure before and after lymphadenectomy and to test the hypothesis that the pressure changes occur before the onset of gynecological cancer-related lymphedema. These changes may be subclinical in nature and may be predictive of the onset of lymphedema.

PATIENTS AND METHODS

Patients

Participants were recruited from the inpatients in the gynecology ward of Keio University Hospital. Patients were screened at admission, and the inclusion criteria were: 1) diagnosis of a gynecological cancer (cervical, uterine, or ovarian); 2) operation including pelvic lymph node dissection; and 3) patient age range from 20 to 80 years. Patients were excluded if they exhibited: 1) cellulitis; 2) leakage of lymphatic fluid; 3) deep venous thrombosis and/or a severe aneurysm; 4) a rating of 0 or 1 using the Eastern Cooperative Oncology Group Performance Status (PS); 5) inability to understand because of cognitive impairment; or 6) refusal to participate.

Study Design

A prospective study was conducted in patients with gynecological cancer to evaluate lymphatic function before and after pelvic lymphadenectomy. Examinations were carried out five times: before (T0) and one (T1), two (T2), three (T3), and six months (T4) after surgery. The study protocol was approved by the Medical Ethics Committee of Keio University School of Medicine according to the guidelines of the Helsinki declaration. All patients provided their informed consent to participate.

Experimental Procedures

Measurements were performed in the supine position after a rest period of 10 min. Then, 0.5 mL of lidocaine hydrochloride (Xylocaine 1%: AstraZeneca Canada Inc., Mississauga, Canada) was injected subcutaneously for local anesthesia in the dorsum of each participant's foot, and 0.3 mL of ICG (Diagnogreen 0.5%; Daiichi-Sankyo, Co., Ltd., Tokyo, Japan) was injected as a fluorescence contrast agent using a 29-gauge needle. Immediately after the injection, real-time fluorescence images of subcutaneous lymph propulsion were obtained with an infrared camera system (PDE™; Hamamatsu Photonics K.K., Hamamatsu, Japan). Both legs were examined, with right and left sequences at random.

Before the ICG injection, a custom-made transparent Riva-Rocci congestion cuff was wrapped around the lower leg just below the popliteal fossa and connected to a standard mercury sphygmomanometer. The cuff pressure was inflated to 70 mmHg. After the subcutaneous injection of ICG, the cuff pressure was gradually deflated at 3-minute intervals by 10-mmHg steps until the fluorescence contrast agent exceeded the upper border of the cuff, indicating that the lymphatic contraction had overcome the cuff pressure, which was defined as the lymph pumping pressure (25,26). Regardless of clinical symptoms, early lymphatic changes was defined as the onset of dermal diffusion (15,19). The reliability of lymph pumping pressure has been reported by two different research groups (18,20).

Leg circumferences were measured at six sites: 20 cm above and below the knee, 10 cm above and below the knee, the ankle, and the dorsum of the foot (around the metatarsophalangeal joints).

Statistical Analysis

For univariate analysis, the demographic data were compared between the early lymphatic changes group and non-lymphedema groups using the Chi-square test. Furthermore, analysis of variance (ANOVA) was performed with the factor of time (before and one, two, three, and six months after the surgery) for the lymph pumping pressure and leg circumference. Data were analyzed with SPSS for Windows (version 18.0, SPSS Inc. Chicago, IL, USA), and p values less than 0.05 were considered significant.

RESULTS

Participants' Characteristics

Between January 2011 and November 2011, 72 patients were screened, and 29 patients (29 women) met the selection criteria and agreed to participate in the study. Of these, 22 (75.9%) completed the five examinations (*Table 1*). Of the 22 patients, aged 25 to 62 years (mean ± SD: 40.6 ± 9.6 years) with a gynecological cancer, 15 had cervical cancer (2 in stage Ia1, T1a1 N0 M0; 12 in stage Ib1, T1b1 N0 M0; 1 in stage Ib2, T1b2 N0 M0), 2 had uterine cancer (1 in stage Ic, T1c M0 N0; 1 in stage IIb, T2b N0 M0), 4 had ovarian cancer (1 in stage Ia, T1a N0 M0; 2 in stage Ic, T1c N0 M0; 1 in stage IIIc, T3c N0 M0), and 1 had combined uterine and ovarian cancer (stage Ia + Ic; T1a N0 M0 + T1c N0 M0). All patients underwent pelvic lymphadenectomy. Staging was based on the International Federation of Gynecology and Obstetrics (FIGO) classification, 1994 revision for cervical cancer (27) and the 1988 revision for uterine (28,29) and ovarian cancers (30) (*Tables 1,2*).

There were no important adverse events or side effects in either group.

Diagnosis of Subclinical Lymphedema

Of the 22 patients, 5 (# 2, 3, 6, 10, 21) (22.7%) were diagnosed as having early lymphatic changes based on the presence of dermal diffusion (*Fig. 1*). There were no significant differences between both groups in the demographic data (age in 10-year age groups, type of cancer, surgical procedure, extent of lymph node dissection, lymph node metastasis, and chemotherapy). (Chi-square test, p = 0.372, 0.540, 0.303, 0.166, 0.589, and 0.076, respectively). There were no clinical findings of pitting edema and skin stiffness over the five examinations during six months of follow-up.

Lymph Pumping Pressure

In the non-lymphedema group (n = 17, 34 lower extremities), the average lymph pumping pressure was 51 ± 19 mmHg at T0, 51 ± 18 mmHg at T1, 53 ± 19 mmHg at T2, 54 ± 20 mmHg at T3, and 44 ± 20 mmHg at T4. The pressure was lower at T4 than preoperatively, but not significantly (ANOVA, p = 0.326).

In the early lymphatic changes group (n = 5; right 1, left 3, bilateral 1), the average lymph pumping pressure was 25 ± 18 mmHg at T0, 58 ± 13 mmHg at T1, 63 ± 8 mmHg at T2, 58 ± 13 mmHg at T3, and 35 ± 21 mmHg at T4. Three patients (# 2, 6, 10) developed

TABLE 1
Patients' Characteristics, Gynecological Cancer Treatment, and Early Lymphatic Changes

Case	Age (years)	Cancer	Stage (FIGO)	Operation	Lymphadenectomy	Lymph node metastases	Treatment		Dermal diffusion	
							Chemotherapy	Radio-therapy	Side	Delay (months)
1	35	cervical	I b1	SRH	PLN	0/32	(-)	(-)		
2	43	cervical	I a1	SRH	PLN	0/34	(-)	(-)	Lt	2
3	38	cervical	I b1	RT	PLN	0/18	(-)	(-)	Lt	6
4	31	cervical	I a1	RT	PLN	0/33	(-)	(-)		
5	39	cervical	I b1	SRH	PLN	0/28	(-)	(-)		
6	38	cervical	I b1	RT	PLN	0/27	(-)	(-)	Lt	3
7	49	uterine +ovarian	I a + I c	TAH + BSO	PLN + PAN + OMT	0/71	TC	(-)		
8	59	ovarian	I c	TAH + BSO	PLN + PAN + OMT	0/48	TC	(-)		
9	35	cervical	I b1	RT	PLN	0/22	(-)	(-)		
10	25	cervical	I b1	RT	PLN	0/40	(-)	(-)	Rt	1
11	33	cervical	I b1	RT	PLN	0/14	(-)	(-)		
12	29	cervical	I b1	RH	PLN	0/42	(-)	(-)		
13	32	cervical	I b1	RT	PLN	0/44	(-)	(-)		
14	46	ovarian	I c	TAH + BSO	PLN + PAN + OMT	0/67	TC	(-)		
15	41	cervical	I b2	RH	PLN	40/50	TP	(-)		
16	47	cervical	I b1	RH	PLN	4/42	CPT-11 + NDP	(-)		
17	28	cervical	I b1	RT	PLN	0/48	(-)	(-)		
18	48	ovarian	III c	TAH + BSO	PLN + PAN + OMT	0/66	TC	(-)		
19	45	uterine	II b	SRH	PLN + PAN + OMT	0/54	CAP	(-)		
20	42	cervical	I b1	RH	PLN	0/27	(-)	(-)		
21	62	uterine	I c	SRH	PLN	0/33	(-)	(-)	Bil	3
22	48	ovarian	I a	TAH + BSO	PLN + PAN + OMT	0/57	TC	(-)		

Abbreviations: RH, radical hysterectomy; SRH, semi-radical hysterectomy; RT, radical trachelectomy; TAH, total abdominal hysterectomy; BSO, bilateral salpingo-oophorectomy; PLN, pelvic lymphadenectomy; PAN, paraaortic lymphadenectomy; OMT, omentectomy; TC, paclitaxel and carboplatin; TP, paclitaxel and cisplatin; CPT-11, irrinotecan; NDP, nedaplatine; CAP, cyclophosphamide and doxorubicin and cisplatin; Rt, right; Lt, left; Bil, bilateral

TABLE 2
Patients' Characteristics, Early Lymphatic Changes, and Findings of Indocyanine Green Fluorescent Lymphography

Case	Edematous feeling of patients						Lymph-ocele	Dermal diffusion		Lymph pumping pressure (mm Hg)				
	Delay		Site					Side	Delay	Delay (months)				
	Short	Long	Abdominal	Inguinal	Pudendal	Femoral			(months)	0	1	2	3	6
1	1 w	(-)	Bil / (-)	Bil / (-)	(-) / (-)	(-) / (-)	(-)			20/10	40/40	40/40	40/50	30/60
2	(-)	4, 5, 6 m	(-) / (-)	(-) / Lt	(-) / (-)	(-) / (-)	(-)	Lt	2	30/40	50/50	60/**70**	60/**70**	20/**20**
3	6 w	5 m	(-) / (-)	(-) / Lt	(-) / (-)	Lt / Lt	Rt	Lt	6	40/40	40/40	60/60	60/50	60/**70**
4	2 d	1, 2, 6 m	(-) / (-)	(-) / Bil	Bil / (-)	(-) / (-)	(-)			30/30	60/60	70/30	70/70	70/70
5	6 d	1, 3 m	(-) / (-)	(-) / (-)	(-) / (-)	Bil / Lt	Bil			30/30	30/50	60/40	70/50	70/ 70
6	5 d	1 m	(-) / Bil	(-) / (-)	(-) / Bil	Bil / Bil	Lt	Lt	3	40/40	70/70	30/50	70/**40**	30/**20**
7	(-)	1 m	(-) / (-)	(-) / (-)	(-) / (-)	(-) / (-)	(-)			70/70	70/70	70/70	70/70	20/10
8	(-)	(-)	(-) / (-)	(-) / (-)	(-) / (-)	(-) / (-)	(-)			40/20	70/60	50/60	60/70	50/50
9	(-)	(-)	(-) / (-)	(-) / (-)	(-) / (-)	(-) / (-)	(-)			60/ 0	70/70	70/70	70/70	40/40
10	(-)	1 m	(-) / (-)	(-) / Rt	(-) / Rt	(-) / (-)	Bil	Rt	1	30/70	**70**/70	**70**/50	**70**/70	**30**/30
11	2 d	1 m	(-) / (-)	(-) / (-)	Rt / Rt	(-) / (-)	(-)			70/60	50/60	50/70	50/40	0/70
12	(-)	(-)	(-) / (-)	(-) / (-)	(-) / (-)	(-) / (-)	(-)			70/70	40/60	70/50	70/70	60/50
13	(-)	1, 2 m	(-) / (-)	(-) / (-)	(-) / Lt	(-) / (-)	(-)			70/70	70/50	60/70	60/70	60/40
14	(-)	(-)	(-) / (-)	(-) / (-)	(-) / (-)	(-) / (-)	Bil			70/70	70/70	70/70	70/70	50/40
15	6 d	1, 2 m	(-) / Rt	Bil / Rt	(-) / Bil	Bil / Rt	(-)			70/70	40/70	40/50	50/30	40/40
16	2 w	3 m	(-) / (-)	(-) / (-)	(-) / Bil	Bil / Lt	(-)			70/70	50/70	50/70	50/60	60/30
17	(-)	(-)	(-) / (-)	(-) / (-)	(-) / (-)	(-) / (-)	(-)			60/50	60/50	70/70	50/70	70/70
18	(-)	6 m	(-) / (-)	(-) / Rt	(-) / (-)	(-) / (-)	Bil			50/40	30/30	10/20	0/20	20/10
19	8 d	3 m	(-) / (-)	Bil / (-)	Bil / Bil	Bil / (-)	(-)			40/30	10/50	20/70	20/20	20/40
20	4, 8 d	1, 3, 5 m	(-) / (-)	(-) / Rt	Bil / Rt	Bil / Rt	(-)			30/50	40/30	50/60	40/50	40/30
21	(-)	2 – 6 m	(-) / (-)	(-) / (-)	(-) / (-)	(-) / Lt	(-)	Bil	3	0/0	30/0	20/0	**60/50**	**20/40**
22	2 d	(-)	(-) / (-)	(-) / (-)	Rt / (-)	Rt / (-)	(-)			40/50	0/30	0/50	50/20	40/50

Abbreviations: m, month; w, week; d, day; Rt, right; Lt, left; Bil, bilateral

Values underlined in bold indicate the lymph pumping pressure when the dermal diffusion appeared.

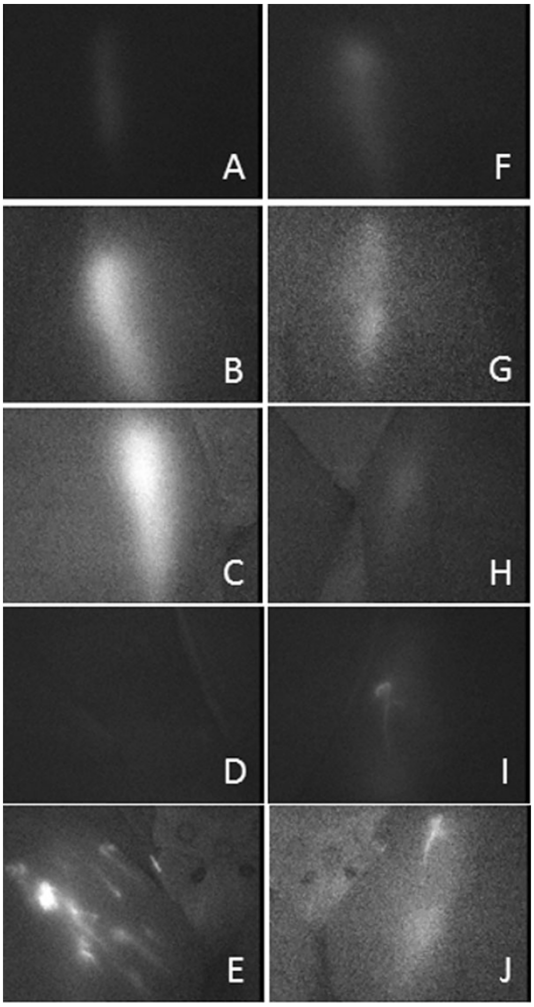

Fig. 1. Typical changes in the fluorescence lymphangiography of patient (no.21) with early lymphatic changes before and after pelvic lymphadenectomy over 6 months of follow-up. A-E) Right proximal femur. Before surgery (A), one month (B), two months (C), three months (D), and six months after surgery (E). F-J) Left proximal femur. Before surgery (F), one month (G), two months (H), three months (I), and six months after surgery (J).

early lymphatic changes after the lymph pumping pressure rose to 70 mmHg at T1, T2, and T3, and one patient (# 21) developed early lymphatic changes bilaterally when the pressure reached 50 and 60 mmHg at T3. Lymph pumping pressure decreased thereafter in these four patients (# 2, 6, 10, 21). One patient (# 3) developed early lymphatic changes when the pressure reached 70 mmHg at T4 (*Table 2, Fig. 2*).

There was a significant difference in the lymph pumping pressure between the early lymphatic changes group (33 ± 21 mmHg) and the non-lymphedema group (51 ± 19 mmHg) at T0 (Student's t-test, p = 0.026).

Leg Circumferences

Significant decreases were found in leg circumferences at the six sites over the six months of follow-up in both groups. In the non-lymphedema group (n = 17, 34 lower extremities), the average leg circumference was 100 ± 0% at T0, 97.5 ± 2.9% at T1, 97.2 ± 3.6% at T2, 97.9 ± 3.5% at T3, and 99.0 ± 3.8% at T4 (Student's t-test, p = 0.000, 0.000, 0.000, and 0.000). In the early lymphatic changes group (n = 5; right 1, left 3, bilateral 1), the average leg circumference was 100 ± 0% at T0, 98.7 ± 2.2% at T1, 99.1 ± 2.7% at T2, 98.9 ± 2.2% at T3, and 100.1 ± 2.8% at T4 (Student's t-test, p = 0.000, 0.015, 0.000, and 0.729).

DISCUSSION

Secondary lymphedema is caused by lymphatic flow return failure after pelvic lymphadenectomy in gynecological cancer patients (24). In chronic lymphedema, lymphatic dysfunction has often become irreversible and resistant to therapy because the structure of the lymph vessels has often been destroyed. To provide effective conservative therapy and surgical interventions, such as lymphatico-venous anastomosis first created by Olszewski and Nielubowicz (31), it is necessary to evaluate not only the morphology of lymph vessels, but also lymphatic function, and to detect reversible lymphatic flow return failure in the early stage of lymphedema.

This is the first report of prospectively observed lymphatic function over time using

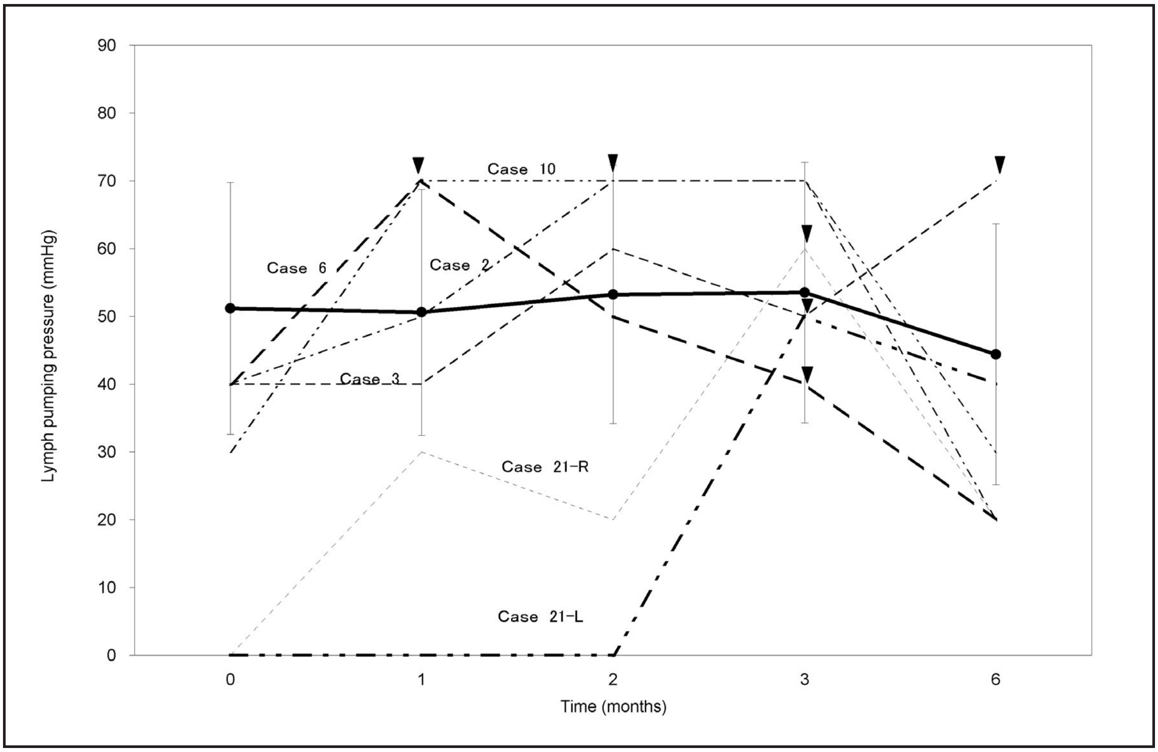

Fig. 2. Changes in the lymph pumping pressure before and after pelvic lymphadenectomy over 6 months of follow-up. The solid line indicates the non-lymphedema patients. Values are expressed as the means ± standard deviation (n = 17). The dashed lines indicate each patient with early lymphatic changes (n = 5, 6 extremities). The horizontal axis shows the time from surgery (months). The vertical axis shows the lymph pumping pressure (mmHg). Closed triangles indicate the time when the dermal diffusion first appeared (no. 2 at T2, no. 3 at T4, no. 6 at T3, no. 10 at T1, no. 21-R at T3, no. 21-L at T3)

lymph pumping pressure (20,21) and the appearance of dermal diffusion (16-18), before and after pelvic lymphadenectomy. In five of the 22 patients, early lymphatic changes were diagnosed based on the dermal diffusion observed with fluorescence lymphangiography. Lymph pumping pressure showed no significant changes as compared with before and after surgery in the non-lymphedema patients, while it increased gradually and dermal diffusion was observed after surgery in all five patients with early lymphatic changes. Subsequently, the pressure decreased in four of the five patients. In one patient (# 3), lymphatic dysfunction was considered to have occurred more slowly than in the other four patients because lymph pumping pressure reached its maximum at 6 months when dermal diffusion appeared.

The direct factor that produces internal lymphatic pressure is contraction of lymph vessels, while indirect factors are internal tissue pressure, tissue osmotic pressure, and venous pressure (22). Direct lymph pressure is much lower than indirect pressure. Olszewski et al reported that systolic lymph end pressure generated by intrinsic contractions of lymphatics ranged between 12 and 70 mmHg, and systolic lymph lateral pressure with free flow was lower and ranged between 5 and 30 mmHg by direct measurement with cannulation in a horizontal position in healthy human legs (32,33). Unno et al reported that, in 30 legs from healthy volunteers, indirect lymph pumping pressure in the sitting position was 29.3 ± 16.0 mmHg (0-60 mmHg) using the Riva-Rocci congestion cuff (18). Lymph pumping pressure was measured as a parameter of maximum lymph pumping ability.

Pathological studies have shown that wall thickening of lymphatic vessels due to proliferation of lymphatic smooth muscle cells results in lymphatic lumen stenosis (18,22-24,34,35). Although this change is reversible in the acute stage, it becomes irreversible in the chronic stage. Reflecting this pathological change, it is hypothesized that the lymph pumping pressure increases in the acute stage and gradually decreases in the chronic stage.

Lymph pumping pressure increased gradually after surgery, and dermal diffusion was observed at the same time in the five cases that developed early lymphatic changes, and then, in four of the five cases, the pressure decreased. This result supports the hypothesis that lymphatic dysfunction, seen as changes in the lymph pumping pressure, occurs earlier than morphological changes of the lymph vessels. This trend indicates that the lymph vessels became dysfunctional and were overwhelmed by the overload condition, and this feature is a useful predictor for the early diagnosis of developing lymphedema.

There was no obvious difference with respect to background factors such as age, type, grade, stage of cancer, or surgical procedure between the early lymphatic changes group and non-lymphedema group. On the other hand, preoperative lymph pumping pressure was significantly lower, suggesting the presence of lymphatic dysfunction, in the early lymphatic changes group.

It is necessary to consider the differential diagnosis of the potential lymphatic dysfunction in primary lymphedema. The causes of primary lymphedema are classified into hypoplasia of lymphatic endothelium or lymphatic valves associated with genetic abnormalities and malformation (hyper or hypoplasia) of lymph vessels without genetic abnormalities (36-39).

The first is accompanied by lymphedematous syndromes, which might be clinically distinguishable from the patient without visible lymphedema. The latter could not be excluded completely. Although there was no abnormal morphology of superficial lymph vessels on fluorescence lymphangiography, information about deep lymph vessels could not be obtained. Patients with malformations of deep lymph vessels might have had lower lymph pumping pressure.

In addition, the distribution of lymph pumping pressure had a wide range in the non- lymphedematous group (before surgery, 0 - 70 mmHg), and even in patients with low pressures. The possibility of developing lymphedema after 6 months of observation cannot be ruled out. To elucidate this problem, longer follow-ups with more participants are needed in the future.

Fluorescence lymphangiography also has a limitation in that it can only obtain emission signals through about a 2 to 3 cm depth of subcutaneous tissue, and it can only be used to evaluate superficial lymph vessels. Deep lymph vessels and spontaneous lymphatico-venous shunts cannot be assessed. In the present study, however, these limitations of fluorescence lymphangiography were not problematic, because dermal diffusion can be detected as abnormal flow in superficial lymphatic capillaries (15-17). ICG lymphangiography has been criticized because the ICG itself may influence lymphatic pumping in animal experiments (40). Though this may not be as important in prospective studies, this potential problem needs to be addressed in future studies.

Fluorescence lymphangiography and manometry, applying the principle of blood pressure measurement, were used as functional assessments of lymphatic vessels (18,20-21). In cross-sectional studies (18,21,22), it was reported that dysfunction of the lymph vessels or a decrease in lymph pumping pressure preceded morphological changes in patients with mild lymphedema. Obtaining information on how the lymph pumping pressure changes longitudinally may lead to the diagnosis of lymphedema at an earlier stage and to identification of the risk of developing lymphedema. However, the "lymphatic congestion method" produced venous hypertension artificially, which caused an increase in tissue fluid pressure by the dilated veins and increased capillary filtration and lymph formation, which increases pre-load (volume load) (41). According to the Frank-Starling law, the lymph vessel increases its pumping function, so that maximum lymph pumping ability can be evaluated. We hypothesize that the maximum lymph pumping pressure will change in the acute stage of lymphedema, and it will be useful to detect the dysfunction of lymph vessels after pelvic lymphadenectomy as an early sign of lymphedema.

The dermal diffusion observed with fluorescence lymphangiography was used as an indicator of the onset of subclinical lymphedema (15-17). Pelvic lymphadenectomy damages the structure of the lymph flow path and increases flow resistance (afterload, pressure load). At first, lymph vessels increase their contractile force to preserve lymphatic flow. If the lymph fluid flow in inadequate, backflow from lymph collectors to superficial lymphatic capillaries occurs, continuing to bypasses. This phenomenon is termed dermal diffusion (21,22,31). Fluorescence lymphangiography is suitable for diagnosing the early onset of lymphedema (15-17,41,42). Dermal diffusion was noted in both lymphscintigraphy and fluorescence lymphangiography, and their findings are generally consistent. The area of the dermal diffusion expands with the progression of lymphedema (13).

In four of the five present cases (# 2, 3, 10, 21), dermal diffusion occurred while the lymph pumping pressure was increasing, which was consistent with an increase in lymph flow resistance. In 1 case (# 6), dermal diffusion occurred while the lymphatic pressure was decreasing followed by an increment. It is unclear why this inversion of order occurred. The reason why lymph pumping pressure did not follow the same course and early lymphatic changes occurred at different intervals after surgery in individual patients is thought to be due to differences in lymphangiogenesis after pelvic lymphadenectomy, including the variation in expression of genes involved in lymphangiogenesis, such as VEGF-C (37,39,43-49), VEGFR3 (37,49), FOXC2 (36,37,39), and SOX18 (37,39,50).

Limb circumference changes in the non-lymphedema group did reduce significantly over the 6 months. This may not be expected and we are uncertain why this occurred. It is obvious that the changes, despite being significant, are small and this may be due to the sample size or normalization of the data. It may also be possible that the patients have chosen healthier lifestyles following their cancer treatment and although data is not available, patients did report weight reductions of 3 to 5 kg after operation and some disuse atrophy which may also be factors. We also found a significant reduction in the early lymphatic change group except for the T4 measurement. These changes were smaller than in the non-lymphedema group and the small sample size may have a direct effect on these values. It might be reasonable to suspect that the lymphatic changes would result in circumference changes, but perhaps the early changes we see with imaging may precede changes in circumference and further following of the patients in future studies could shed light on this hypothesis.

The limitations of the present study are its small sample size and the limited observation period, which precluded the inclusion of patients who developed lymphedema after six months postoperatively. It is necessary to perform a study with a larger sample size and longer follow-up than this pilot study.

The number of participants in the present study was small, in part because it included a clear definition of the diagnostic criterion of asymptomatic lymphedema in the early stage as the occurrence of dermal diffusion, and then the patients were observed prospectively. Niikura et al. (51) reported that new symptomatic lymphedema was identified in 5 of 12 patients who underwent systematic lymphadenectomy during 38 months of observation of 35 consecutive patients with cervical cancer. Therefore, in comparison, 29 of 72 participants assessed for eligibility in the present study is a reasonable number. However, in order to obtain more definite conclusions, a large-scale, multi-center, prospective study is needed.

Another limitation of the present study was the dropout rate (7 of 29 patients, 24.1%). The reasons for the dropouts were patient refusal in six and lack of data in one. The dropout rate may be a problem in this type of study because the patients must participate for a long period of time (6 months). Thus, greater efforts are needed to reduce this dropout rate.

CONCLUSIONS

In conclusion, a decrease in the lymph pumping pressure subsequent to its excessive increase is considered to be useful as a sign indicating the potential risk of developing lymphedema after pelvic lymphadenectomy.

ACKNOWLEDGMENTS

The authors would very much like to thank Naoki Unno, M.D., at Hamamatsu Medical University. The authors are also grateful to Hideyuki Saya, M.D. and Toru Takebayashi, M.D., at Keio University, for their valuable discussions.

Part of this study was funded by the Japanese Funding Program for Training for Oncology Professionals in 9 universities, Ministry of Education, Culture, Sports, Science and Technology, Japan (project number: 05-067-0034).

The authors have declared that no competing interests exist.

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