CARDIOPULMONARY SUPPORT AND PHYSIOLOGY

THE INFLUENCE OF HUMAN T LYMPHOTROPIC VIRUS TYPE I INFECTION ON THE OUTCOME OF CARDIOVASCULAR SURGERY

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Objective: Human T lymphotropic virus type I infects CD4⁺ T cells and affects cell-mediated immunity. Cardiopulmonary bypass transiently alters lymphocyte subsets, resulting in a reduction in CD4⁺ T cells and an increase in CD8⁺ T cells. We proposed that cardiovascular operations and human T lymphotropic virus type I infection may act synergistically, resulting in serious damage to cell-mediated immunity.

Methods: A total of 517 consecutive patients who were preoperatively screened for anti-human T lymphotropic virus type I antibody and underwent cardiovascular operations with cardiopulmonary bypass were enrolled in this study. Of the 517 patients, 82 (16%) had positive test results for anti-human T lymphotropic virus type I antibody. The surgical outcome of patients with positive and negative results for anti-human T lymphotropic virus type I antibody was analyzed retrospectively.

Results: There was no difference between the 2 groups with respect to early mortality. Distribution of survival curve was also not significantly different ($P = .5$; mean follow-up duration, 2.4 ± 1.8 years [range, 0-9.4 years] and 3.2 ± 2.8 years [range, 0-9.8 years]) in the groups with positive and negative antibody results, respectively). In particular, long-term follow-up did not reveal adult T-cell leukemia or human T lymphotropic virus type I-associated myelopathy, and occurrence of neoplasm did not differ between groups. Early infectious complication was, however, significantly higher in the group with positive antibody results than in the group with negative results ($P = .02$). Logistic regression analysis revealed human T lymphotropic virus type I infection as a significant risk for this complication ($P = .04$; odds ratio, 2.5; 95% confidence interval, 1.0-5.8).

Conclusion: A combination of human T lymphotropic virus type I infection and cardiovascular operation is believed to increase the potential risk of infectious complications shortly after the operation. However, this synergistic effect seems to be transient and has little influence on long-term prognosis. (J Thorac Cardiovasc Surg 2000;120:699-706)

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Human T lymphotropic virus type I (HTLV-I) infects CD4⁺ T cells and causes adult T-cell leukemia (ATL) and HTLV-I-associated myelopathy/tropical spastic paraparesis (HAM/TSP). In addition, several disorders have been associated with HTLV-I, including chronic pulmonary disease, chronic renal failure, uveitis, opportunistic infection, and neoplastic growth. Although the precise mechanisms of development are unclear, these disorders are considered to be manifestations of HTLV-I-altered cellular immunity.¹⁻⁸ Two observations prompted our investigation: (1) symptom-

Table I. Preoperative and operative factors of the patients

Variables	Anti-HTLV-I antibody		P value
	Positive (n = 82)	Negative (n = 435)	
Age (y)	65 (56-70)	63 (54-69)	.2
Weight (kg)	50 (45-59)	53 (47-61)	.2
Sex (M/F)	38/44	256/179	.04
Preoperative complications			
Diabetes (%)	4 (5)	33 (8)	.4
Cerebral infarction (%)	1 (1)	22 (5)	.1
Renal failure (%)	2 (2)	13 (3)	.8
Pulmonary disease (%)	2 (2)*	4 (1)	.2
Neoplasm (%)	1 (1)	7 (2)	.8
Others (%)	2 (2)	10 (2)	.1
Time of operation			
March 1989–February 1995 (%)	40 (49)	259 (60)	.1
March 1995–February 1999 (%)	42 (51)	176 (40)	
Emergency (%)	8 (10)	25 (6)	.2
Redo (%)	2 (2)	18 (4)	.8
Procedures			
CABG (%)	14 (17)	114 (26)	.1
Valve replacement or valvuloplasty (%)	37 (45)	183 (42)	.6
Intracardiac repair of anomaly (%)	8 (10)	45 (10)	.9
Repair of thoracic aortic aneurysm (%)	17 (21)	71 (16)	.3
Others (%)	6 (7)	22 (5)	.4
CPB time (min)	147 (108-188)	150 (122-187)	.3
Aortic crossclamp time (min)	93 (67-126)	88 (71-116)	.9

Data are given as median (25th-75th percentile) where shown. CABG, Coronary artery bypass grafting.

*Includes a patient with suspected HTLV-I-associated bronchopneumopathy.

free carriers of HTLV-I are reported to have subclinical evidence of impaired cell-mediated immunity,^{3,4} and (2) cardiopulmonary bypass (CPB) is known to affect cellular immunity,⁹⁻¹⁵ with changes in lymphocyte subsets, including a reduction in CD4⁺ T cells and an increase in CD8⁺ T cells, being common findings. Therefore, if patients infected with HTLV-I were to undergo cardiovascular operations, there may be a synergistic risk of serious damage to cell-mediated immunity, thus increasing susceptibility to infection, neoplasms, and other immune disorders. Few studies have investigated this matter, probably because local HTLV-I infection is not typically endemic, and thus the patient pool with HTLV-I is too small. Our institute, however, is located in the southern Japanese island of Kyushu where HTLV-I infection is endemic, and we have observed 219 (15%) HTLV-I carriers in 1470 surgical patients (including general operations) since 1989. In the present study we retrospectively investigated the influence of HTLV-I infection on the outcome of cardiovascular operations.

Patients and methods

We introduced preoperative screening for the antibody to HTLV-I by using an enzyme immunoassay (EIA; New Eitest-ATL; Eisai, Tokyo, Japan) in March 1989. Our subject popu-

lation consisted of 517 consecutive patients who were screened for anti-HTLV-I antibody between March 1989 and February 1999. All patients underwent cardiovascular operations with CPB. Among these patients, 82 (16%) had positive results for anti-HTLV-I antibody (HTLV-I⁺), and 435 (84%) had negative results (HTLV-I⁻).

Surgery consisted of valve replacement, valvuloplasty, coronary artery bypass grafting, intracardiac repair of a simple anomaly, and graft replacement of the thoracic aortic aneurysm. After systemic heparinization, moderate-to-deep hypothermic CPB was performed by means of a hollow-fiber membrane oxygenator. Circulatory arrest with deep hypothermia or selective cerebral perfusion was used for cerebral protection in the aortic arch and descending aortic repair. Myocardial protection was achieved by means of cold blood cardioplegia, as well as topical myocardial cooling with cold saline solution. Before discontinuation of CPB, all patients were warmed to a rectal temperature of 36°C or more. The heparin effect was neutralized by protamine sulfate until the activated coagulation time had normalized.

All postoperative complications were recorded. Cardiac complications included any heart failure requiring high-dose catecholamines or mechanical circulatory supports. Pulmonary complications included all those resulting in prolonged mechanical ventilation. Renal complications were those necessitating hemodialysis. Infectious complication was defined as any occurrence of mediastinitis, pneumonia, deep wound infection, or sepsis that necessitated prolonged

Table II. Early death and complication

		Anti-HTLV-I antibody		P value
		Positive (n = 82)	Negative (n = 435)	
Causes of death (%)	Cerebrovascular accident	2 (2.5)	6 (1.4)	.2
	Heart failure	0 (0)	12 (2.8)	.1
	Infection*	1 (1.2)	5 (1.1)	.9
	Multiple organ failure	1 (1.2)	3 (0.7)	.6
	Others	1 (1.2) [†]	3 (0.7)	.6
Complications (%)	Infection*	8 (9.7)	17 (3.9)	.02
	Heart failure	2 (2.4)	18 (4.1)	.5
	Cerebrovascular accident	2 (2.4)	13 (3.0)	.8
	Respiratory failure	3 (3.7)	7 (1.6)	.2
	Renal failure	2 (2.4)	5 (1.1)	.4
	Others	7 (8.5)	17 (3.9)	.07

*Infection indicates mediastinitis, sepsis, pneumonia, or deep wound infection.

[†]A case of GVHD.

antibiotic therapy. Early morbidity and mortality were defined as complication or death occurring during the admission period after an operation. Any event occurring after discharge was defined as a late event. Follow-up information was obtained by reviewing patient medical records or by direct telephone contact. Questions were asked about the cause and date of death, the patient's condition, autonomy, medical treatment, and whether any signs of myelopathy, uveitis, or respiratory disorders were present. Mean follow-up duration was 2.4 ± 1.8 years (range, 0-9.4 years) for HTLV-I⁺ patients and 3.2 ± 2.8 years (range, 0-9.8 years) for HTLV-I⁻ patients.

All statistical analyses were conducted by means of JMP Statistical Discovery Software (SAS Institute, Inc, Cary, NC). Data are expressed as median and 25th and 75th percentiles. Differences between the groups were determined by the Mann-Whitney *U* test and the Fisher exact test. Survival data were analyzed by standard Kaplan-Meier actuarial techniques for estimation of survival probability. We also examined the early and late postoperative events to analyze the temporal relation between operations and manifestation of HTLV-I infection. However, this analysis, especially for late events, is limited in its interpretation because these events are time-related subjects and are too diverse to be dealt with as simple proportions. In addition, the present study is not randomized and involves a problem of dissimilarities of the groups. Because of these limitations and risks, we also examined the influences of preoperative and operative risk factors on surgical outcomes with a logistic regression analysis.

This study was conducted along with guidelines for human research by the Ethics Committee at Kagoshima University Faculty of Medicine, and informed consent was obtained from all patients.

Results

Background factors, including age, body weight, and preoperative complications, were similar for both

HTLV-I⁺ and HTLV-I⁻ groups, although the proportion of female subjects was significantly larger in the HTLV-I⁺ group than in the HTLV-I⁻ group. The data also included an HTLV-I⁺ patient with suspected HTLV-I-associated bronchopneumonopathy. Moreover, the time of the operation, emergency or redo status, procedures, duration of CPB, and aortic crossclamping were also similar between the 2 groups (Table I).

Early mortality did not differ significantly between the 2 groups (5/82 HTLV-I⁺ patients (6%) and 29/435 HTLV-I⁻ patients (7%), $P = .9$). There was no significant difference in the distribution of causes of early death, such as cerebrovascular accident, heart failure, and sepsis, although a case of graft versus host disease (GVHD) was observed in the HTLV-I⁺ group (Table II).

Early complications occurred in 24 (29%) of 82 patients in the HTLV-I⁺ group compared with 77 (18%) of 435 patients in the HTLV-I⁻ group. This difference was statistically significant ($P = .02$). In particular, the occurrence of infectious complications was significantly higher in the HTLV-I⁺ group than in the HTLV-I⁻ group ($P = .02$). The other complications, heart failure, cerebrovascular accident, renal failure, and respiratory failure, occurred without significant differences between the groups (Table II).

The factors thought to be risks for infection, such as age, sex, diabetes, renal failure, and conditions of the operation, including HTLV-I infection, were then examined by logistic regression analysis. This revealed anti-HTLV-I antibody positivity as the only significant risk factor for infectious complication ($P = .04$; odds ratio [OR], 2.5; 95% confidence interval [CI], 1.0-5.8). Emergency status tended to be another risk ($P = .07$; OR, 1.6; 95% CI, 0.8-7.2). The other factors did not exert significant influences on this complication.

Fig 1. Late survival of HTLV-I⁺ and HTLV-I⁻ groups. Early deaths are not included. Follow-up durations are expressed as means and SD (*a* and *b*) and medians with 25th to 75th percentiles, respectively. Difference of distributions between the 2 groups was not significant (*P* = .5).

Table III. Late death and complication

	Anti-HTLV-I antibody	Positive	Negative	P value
Causes of death (%)	Cardiac events	5 (72)	8 (32)	.3
	Cerebrovascular accident	1 (14)	5 (20)	
	Neoplasm	1 (14)	1 (4)	
	Infection	0 (0)	5 (20)	
	Aneurysmal rupture	0 (0)	3 (12)	
	Unknown	0 (0)	3 (12)	
	Total	7 (100)	25 (100)	
Complications (%)	Cerebrovascular accident	1 (33)	2 (15)	.3
	Neoplasm	0 (0)	3 (23)	
	Pulmonary disease	0 (0)	3 (23)	
	Exaggeration	2 (67)	2 (15)	
	Others	0 (0)	3 (23)	
	Total	3 (100)	13 (100)	

There was no significant difference in the microorganisms identified for the 2 groups (*P* = .8). Methicillin-resistant *Staphylococcus aureus* was a major causative microorganism in both groups, affecting 4 (50%) of 8 HTLV-I⁺ patients and 9 (52%) of 17 HTLV-I⁻ patients. As to fungus infection, corresponding figures were 1 (13%) of 8 patients and 1 (6%) of 17 patients, respectively.

Because late events were influenced by many time-related factors, we described only the proportion of events (Table III). Late death was observed in 7 of 77 patients in the HTLV-I⁺ group and 25 of 406 patients in the HTLV-I⁻ group. The major cause of late death was

cardiac event in each group, and composition of the causes was similar between the groups (*P* = .3). There was no significant difference in distribution of late survival between the HTLV-I⁺ and the HTLV-I⁻ groups (Fig 1; *P* = .5; 2.5 ± 1.6 vs 3.4 ± 2.8 follow-up years, respectively). Late complications occurred in 3 of 77 patients in the HTLV-I⁺ group and 13 of 406 patients in the HTLV-I⁻ group. In the HTLV-I⁺ group ATL, HAM/TSP, or uveitis was not seen. There was no significant difference in late complication (*P* = .3). Distribution of the event-free curve was also similar between the groups (Fig 2; *P* = .2; 2.6 ± 1.7 vs 3.4 ± 2.8 follow-up years, respectively).

Fig 2. Event-free survival of HTLV-I⁺ and HTLV-I⁻ groups. Early complications are not included. Follow-up durations are expressed as means and SD (*a* and *b*) and medians with 25th to 75th percentiles, respectively. Difference of distributions between the 2 groups was not significant (*P* = .2).

Ten risk factors, including age, body weight at the operation, sex, anti-HTLV-I antibody positivity, diabetes mellitus, renal failure, time of the operation, emergency or redo status, and CPB time were examined by logistic regression analysis (Table IV). Emergency status was a major risk for early death (*P* < .01; OR, 8.4; 95% CI, 3.2-21.8) and early complication (*P* < .01; OR, 3.2; 95% CI, 1.4-6.9). Interestingly, the analysis showed anti-HTLV-I antibody positivity also as a significant risk for early complication (*P* < .01; OR, 2.2; 95% CI, 1.2-4.0). There was no significant risk concerning late death. Causative risk for late complication was only redo operation (*P* = .03; OR, 10.6; 95% CI, 1.3-89.2).

There were 2 cases in which HTLV-I involvement was suspected. A 68-year-old man in whom HTLV-I-associated bronchopneumonopathy was suspected before the operation had respiratory distress, and analysis showed he had a high titer level of anti-HTLV-I antibody. In addition, atypical lymphocytes similar to ATL cells appeared in his peripheral blood. He had no further development of disease and his condition remained stable for 3.3 years after coronary artery bypass grafting. Another patient was a 24-year-old woman who died of GVHD 32 days after aortic and mitral valve replacement. She and her parents were HTLV-I carriers. In the HLA typing with her parents and sister, 2 unmatched antigens of class II were exhib-

ited in her lymphocyte sample, but all class I antigens, which are usually involved in posttransfusion GVHD, were matched. In addition, Y-chromatin was not detected in her lymphocytes, and pancytopenia was not proven (data not shown).

Discussion

HTLV-I carrier population is usually 0.02% to 0.04% in nonendemic areas. In regions where it is endemic, such as the southern Japanese island of Kyushu, it is 12% to 27%.^{3,16,17} Our institute is located in this area, and the HTLV-I carrier population is 15%. This high prevalence made it possible to observe sufficient numbers of HTLV-I carriers to permit statistical analysis.

Because EIA screening could generate both false-positive and false-negative results, HTLV-I infection was usually confirmed by Western blotting.^{16,17} Together with improved purification of the HTLV-I antigen and improved methods, the difference between recent EIA and Western blotting has been reduced. The sensitivity and specificity of the EIA used in the present study is reportedly 100% and 99% to 100%, respectively.¹⁸ Although we could not apply the 2-step method in this study, the diagnostic results are considered to be comparable with those of Western blotting.

As forementioned, this study is not randomized and involves a risk of dissimilarities between the 2 groups. Actually, female dominance in HTLV-I⁺ patients was

Table IV. Logistic regression analysis of risk factors for early and late events

Variables	Early death		Early complication	
	OR (95% CI)	P value	OR (95% CI)	P value
Age (y)	1.1 (0.7-1.7)	.02	1.0 (1.0-1.1)	<.01
Body weight (kg)	1.0 (0.6-1.5)	.2	1.0 (1.0-1.0)	.2
Sex (M/F)	0.6 (0.3-1.6)	.3	0.8 (0.4-1.3)	.3
HTLV-I (positive/negative)	0.9 (0.3-2.8)	.9	2.2 (1.2-4.0)	<.01
Diabetes (yes/no)	—	—	0.6 (0.3-1.2)	.1
Renal failure (yes/no)	0.5 (0.2-1.0)	.06	1.9 (1.1-3.4)	.03
Time of operation (≤February 1995/March 1995≤)	0.3 (0.1-0.8)	.02	0.7 (0.4-1.2)	.2
Emergency operation (yes/no)	8.4 (3.2-21.8)	<.01	3.1 (1.4-6.9)	<.01
Redo operation (yes/no)	2.4 (0.4-13.8)	.3	1.3 (0.3-4.5)	.7
CPB time (min)	1.0 (1.0-1.0)	<.01	1.0 (1.0-1.0)	<.01

Diabetes and renal failure are preoperative complications. —, Variables are unstable for analysis.

significant. Therefore, the limitation deriving from dissimilarities of the HTLV-I⁺ and HTLV-I⁻ group should be taken into account when comparing the 2 groups. We then analyzed the influence of sex by the logistic regression test and found that it had little effect on the surgical outcome. The female dominance is correspondent with previous reports. Although the high mortality of male carriers may cause it, the precise mechanism is still not known.

Previous reports have indicated subclinical evidence of impaired cell-mediated immunity in asymptomatic HTLV-I carriers.^{3,4} HTLV-I-infected CD4⁺ T cells express viral epitopes in the context of their major histocompatibility complex (MHC) class I, which activate MHC class I-restricted antiviral CD8⁺ cytotoxic T cells.⁶ Bernal and colleagues³ hypothesized that the activated CD8⁺ T cells suppress the infected CD4⁺ T cells or, alternatively, that HTLV-I directly decreases the proliferative potential of CD4⁺ T cells, such as occurs in acquired immunodeficiency syndrome. Consequently, lymphocyte subsets may be altered by a reduction in the CD4⁺ T-cell count and an elevation in the CD8⁺ T-cell count.

We must also consider how the immune system is affected under such circumstances. CPB is known to induce alterations in cell-mediated immunity, a reduction in CD4⁺ T cells, an increase in CD8⁺ T cells, and a decrease in natural killer cell cytotoxic activity.⁹⁻¹⁵ Alterations are common but transient, generally lasting only 3 to 4 days postoperatively.⁹⁻¹⁵ However, this temporal effect may be crucial to the CD4⁺ and CD8⁺ T cells already infected by HTLV-I. Under this assumption, synergistic impairment of the immune system should appear during the early postoperative period. In the present study the incidence of infectious complications, such as sepsis, mediastinitis, deep wound infection, and pneumonia, were sig-

nificantly higher in the HTLV-I⁺ group. In addition, risk factors except anti-HTLV-I antibody positivity and emergency status could not reveal significant influences on the infectious complication through logistic regression analysis. Although methicillin-resistant *Staphylococcus aureus* was the major microorganism seen, fungus was also observed. On the other hand, there was no significant influence of HTLV-I infection on late mortality and morbidity. These findings suggest a temporary impairment in immune response. Further examination into perioperative alterations of lymphocyte subsets in HTLV-I⁺ patients is necessary to clarify the precise process.

Individuals infected with HTLV-I reportedly have an estimated 4% lifetime risk of either ATL or HAM/TSP.¹⁹ However, the precise mechanism through which neurologic symptoms, another a neoplastic condition, develop in 1 group of HTLV-I⁺ individuals while the majority remain asymptomatic remains unclear.^{5,7}

Incidence of ATL development is only about 1 of 1200 carriers every year. In addition, it generally takes about 50 years for an asymptomatic HTLV-I carrier to manifest overt ATL.⁸ To date, there have been no reports of this type of leukemia developing after a cardiovascular operation in HTLV-I⁺ patients. On the other hand, manifestation of ATL under long-term immunosuppressive therapy has been reported in renal transplantation.⁸ The authors proposed that immunosuppression shortens the duration of the asymptomatic carrier state. Thus, severe and sustained immune impairment appears to be an important factor in the progression of adult T-cell leukemia.

Two cases of HAM/TSP have been reported.²⁰ These patients manifested HAM/TSP 1 and 2 years after their cardiac operations, respectively. Although preoperative HTLV-I infection was not addressed, the authors proposed that the cause of infection was allo-

Late death			Late complication		
OR (95% CI)		P value	OR (95% CI)		P value
1.0	(1.0-1.1)	.07	1.1	(0.9-1.2)	<.01
1.0	(0.9-1.0)	.2	1.0	(1.0-1.1)	.4
0.4	(0.2-0.9)	.04	0.5	(0.1-1.9)	.3
1.8	(0.7-4.5)	.2	1.3	(0.3-6.6)	.7
—	—	—	0.6	(0.3-1.3)	.2
0.5	(0.2-0.9)	.03	—	—	—
0.5	(0.2-1.2)	.1	0.4	(0.1-1.4)	.1
1.2	(0.3-5.7)	.8	—	—	—
1.1	(0.1-9.5)	.9	10.6	(1.3-89.2)	.03
1.0	(1.0-1.0)	.05	1.0	(1.0-1.0)	.4

genic HTLV-I⁺ blood transfusion. Before the introduction of HTLV-I screening, we experienced a similar case in which the patient developed HAM/TSP 1 year after mitral valve replacement (not reported). Because seroconversion to HTLV-I actually occurs after allogenic blood transfusion, HTLV-I may have caused HAM/TSP in these patients.^{16,17} However, whether HAM/TSP develops in HTLV-I carriers after an operation remains unclear. In the present study a patient with suspected HTLV-I-associated bronchopneumonopathy showed no progression of disease for 3.3 years. Overall, progression of HTLV-I-associated disorders does not appear to occur frequently in HTLV-I⁺ cardiovascular operations.

GVHD typically occurs because of allogenic blood transfusion and has the following characteristic features: new antigen appearance in HLA class I antigen, pancytopenia, and occasional acquisition of Y-chromatin in female patients. Our patient exhibited neither pancytopenia nor Y-chromatin, but 2 unmatched antigens of class II in the patient's lymphocyte sample were observed. These findings appear to differ from typical post-transfusion GVHD. HTLV-I is known to express alien antigens to the MHC on the lymphocyte. Graft-versus-host reaction was subsequently proposed to be induced by HTLV-I, which was activated to provoke the alien HLA antigens under the immunocompromised state.²¹ We have encountered only 1 GVHD case (1.2%) of 82 HTLV-I⁺ cardiovascular surgical patients (1 [0.46%] of 219 HTLV-I⁺ surgical patients). The frequency of GVHD is higher than that of post-transfusion GVHD. However, there are few reports of such GVHD cases in the literatures. We cannot comment further about this matter with little experience and no supportive reports.

In conclusion, the combination of HTLV-I infection and a cardiovascular operation appears to increase

the risk of infectious complications in the early post-operative period. However, this synergistic effect seems to be transient and has little influence on long-term prognosis.

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