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ORIGINAL ARTICLE
Imaging

Temporal Change in Longitudinal Strain After Domino Liver Transplantation With Liver Grafts Explanted From Patients With Hereditary Amyloidogenic Transthyretin Amyloidosis

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Background: Using transthoracic echocardiography, including 2D speckle tracking imaging (STI), this study examined cardiac function after domino liver transplantation (DLT) with liver grafts explanted from patients with hereditary amyloidogenic transthyretin amyloidosis.

Methods and Results: In all, 14 patients who underwent DLT at Kumamoto University Hospital and for whom 2D STI information was available were enrolled in the study; time-dependent echocardiographic changes were evaluated in 7. Although left ventricular (LV) systolic and diastolic function did not differ between the pre- and post-DLT periods (mean [±SD] 5.4±1.0 years after DLT), there were significant ($P<0.05$ for all) increases in the post- vs. pre-DLT period in basal longitudinal strain (LS; −13.4±2.3 vs. −19.3±4.4), relative apical LS index (=apical LS/[basal LS+mid LS]; 0.75±0.20 vs. 0.58±0.08), and LV ejection fraction/global LS (3.91±0.58 vs. 3.06±0.44). Age at the time of DLT was significantly higher in the group with impaired (>−14%) than preserved basal LS (57.2±3.5 vs. 39.6±16.0 years; $P<0.05$). When control subjects (n=14) were added to the enrolled DLT recipients, multivariable logistic regression analysis revealed that a history of DLT was significantly associated with impaired basal LS (>−14%; odds ratio 28.39, 95% confidence interval 1.89–427.45, $P<0.05$).

Conclusions: LV systolic and diastolic function was preserved in the long term after DLT. However, 2D STI revealed subtle cardiac dysfunction in DLT recipients, which may be an early manifestation of cardiac amyloidosis.

Key Words: 2D speckle tracking imaging; Domino liver transplantation; Hereditary amyloidogenic transthyretin amyloidosis; Longitudinal strain; Transthoracic echocardiography

Hereditary amyloidogenic transthyretin (ATTRv) amyloidosis is often first detected in patients during their 20 s and 30 s. There is a gradual progression in symptoms, such as sensory dominant neuropathy, autonomic dysfunction, and cardiac dysfunction, with a mean survival of approximately 10 years without treatment.[1,2] Liver transplantation, which inhibits the production of variant transthyretin (TTR), was conducted as a radical therapy for ATTRv in 2,136 cases from 1990 to 2015.[3] Liver function in patients with ATTRv is usually normal, even though the liver produces variant TTR. Thus, livers removed from patients with ATTRv have been used for

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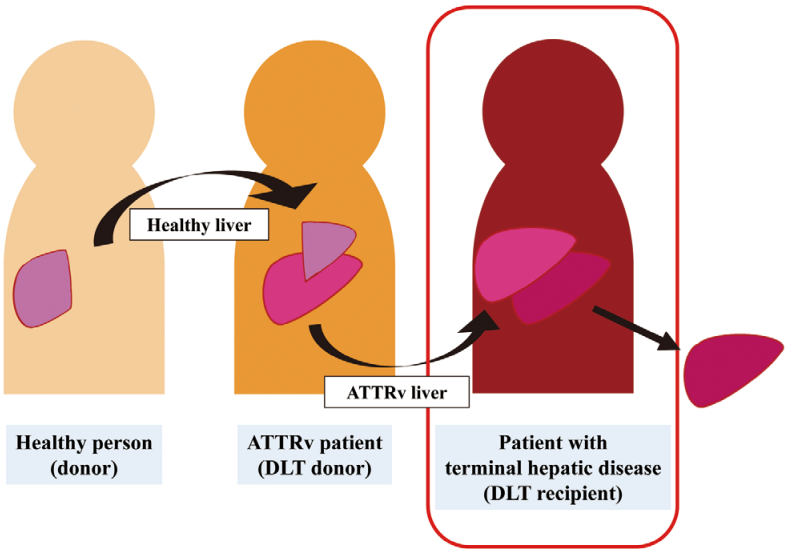

Figure 1. Schematic showing domino liver transplantation (DLT). DLT recipients were enrolled in the present study. ATTRv, hereditary amyloidogenic transthyretin amyloidosis.

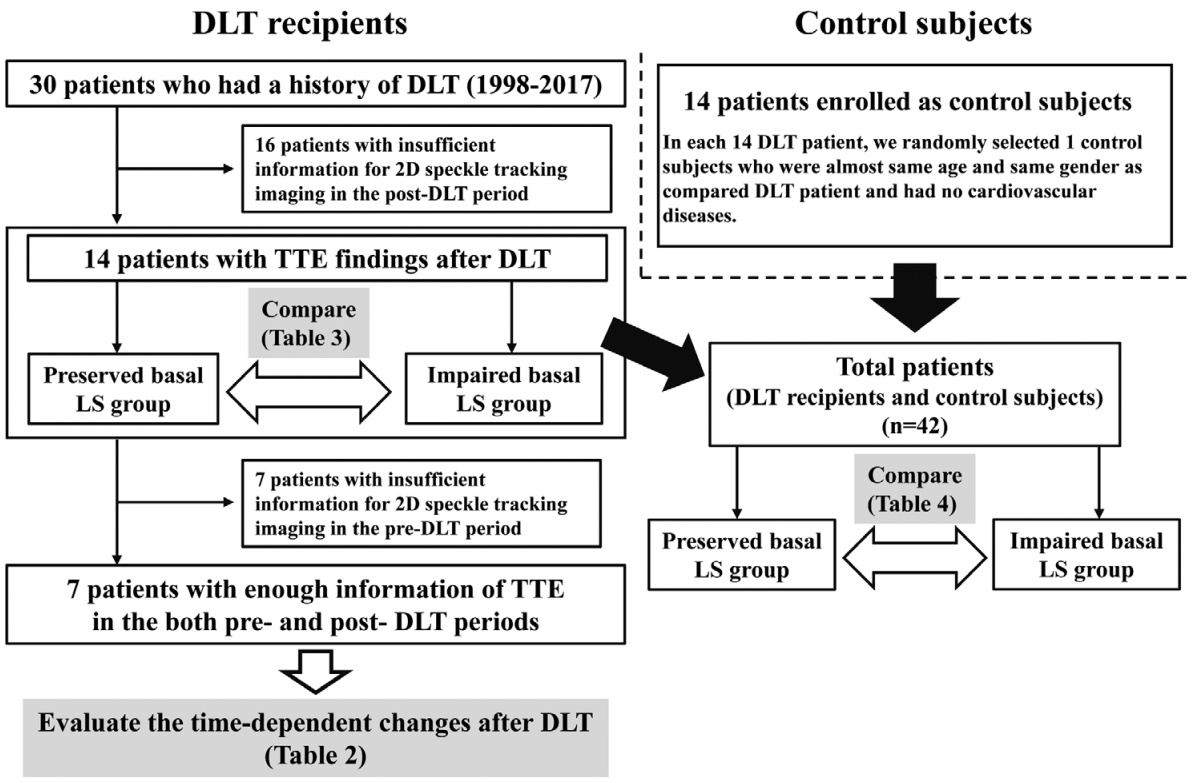

Figure 2. Study flow chart detailing the inclusion and exclusion criteria for study patients. DLT, domino liver transplantation; LS, longitudinal strain; TTE, transthoracic echocardiography.

domino liver transplantation (DLT) to save the lives of patients with end-stage liver disease who have no other appropriate donor liver (**Figure 1**).

Although amyloidosis after receiving a liver allograft donated by a patient with ATTRv has been established,[4] there are only a few case reports of TTR amyloid cardiomyopathy (ATTR-CM) after DLT.[5,6] Thus, the safety of DLT has not been fully evaluated in the heart. The hallmarks of ATTR-CM on transthoracic echocardiography (TTE) are increased left ventricular (LV) thickness, left atrial

Table 1. Clinical Characteristics of DLT Recipients

Patient no.	Sex	Age at time of DLT (years)	Donor TTR mutation	Primary liver disease	Age at time of TTE (years)		Observation period after DLT (years)	Amyloid deposition in heart	Amyloid deposition in organs other than heart
					Pre-DLT	Post-DLT			
1	F	50	Val30Met	PBC	N/A	60	10	N/A	–
2	F	23	Val30Met	BA	N/A	35	11	N/A	–
3	M	44	Val30Met	LC	44	52	9	N/A	+
4	M	56	Val30Met	LC	56	65	9	N/A	+
5	M	55	Val30Met	LC	55	61	7	N/A	+
6	M	63	Val30Met	Hepatitis C	63	67	4	N/A	–
7	M	60	Val30Met	Hepatitis C	60	63	3	N/A	–
8	M	36	Val30Met	LC	N/A	50	14	N/A	+
9	M	60	Ser50Ile	LC	N/A	75	15	+	+
10	F	36	Val30Met	CAPV	N/A	47	11	N/A	+
11	M	59	Val30Met	Hepatitis C	N/A	68	9	N/A	+
12	M	19	Val30Met	BA	N/A	28	9	N/A	+
13	M	60	Val30Met	PSC	60	64	4	N/A	+
14	M	55	Val30Met	LC	55	57	3	N/A	N/A

	Positive for ^{99m}Tc-PYP	Age at time of ^{99m}Tc-PYP (years)	Pacemaker implantation	Dialysis	Aortic stenosis	HF	MI	CV death	Alive or dead
1	N/A	N/A	–	–	–	–	–	–	Dead
2	N/A	N/A	–	–	–	–	–	–	Alive
3	–	53	–	–	–	–	–	–	Alive
4	–	64	–	–	+	+	–	–	Alive
5	–	62	–	–	–	–	–	–	Alive
6	N/A	N/A	–	–	–	–	–	–	Alive
7	–	66	–	–	–	–	–	–	Alive
8	–	50	–	–	–	–	–	–	Alive
9	+	70	–	+	–	+	–	+	Dead
10	–	48	–	+	–	–	–	–	Alive
11	–	68	–	–	–	–	–	–	Alive
12	N/A	N/A	–	–	–	–	–	–	Alive
13	–	63	–	–	–	–	–	–	Alive
14	N/A	N/A	–	–	–	–	–	–	Alive

BA, biliary atresia; CAPV, congenital absence of the portal vein; CV, cardiovascular; DLT, domino liver transplantation; F, female; HF, heart failure; LC, Liver cirrhosis; M, Male; MI, myocardial infarction; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; ^{99m}Tc-PYP, technetium pyrophosphate; TTE, transthoracic echocardiography; TTR, transthyretin.

(LA) enlargement, and reduced systolic and diastolic LV function.[7,8] However, these findings can also be present in other disorders with increased afterload. The longitudinal strain (LS) pattern obtained by 2D speckle tracking imaging (STI) can be used to distinguish ATTR-CM from other causes of LV hypertrophy (LVH).[9,10]

The aim of the present study was to clarify both the time-dependent changes in cardiac function after DLT and the characteristics of cardiac impairment after DLT as evaluated using TTE, including 2D STI.

Methods

DLT Recipients and Control Subjects

Between 1998 and 2017, 30 patients with primary biliary cholangitis, biliary atresia, liver cirrhosis, hepatitis C, congenital absence of the portal vein, or primary sclerosing cholangitis underwent DLT with liver grafts obtained from ATTRv patients and were followed-up at Kumamoto University Hospital. Of these DLT recipients, 16 were excluded from the present study because of insufficient information regarding 2D STI evaluation in the post-DLT period. Thus, 14 DLT recipients were enrolled in this study. Of these 14 DLT recipients, 7 underwent TTE in both the pre- and post-DLT periods. Therefore, time-dependent changes in TTE findings were analyzed in these patients (**Figure 2**). In addition, randomly selected age- and sex-matched patients undergoing TTE at around the same time (i.e., month) as the 14 DLT recipients during the post-DLT period were included in the present study as controls. The 14 control subjects had no cardiovascular diseases, including ischemic heart diseases, valvular diseases, cardiomyopathy, or arrhythmias.

The study protocol conformed to the principles of the Declaration of Helsinki, and was approved by the Institutional Review Board of Kumamoto University (Reference no. 1588). This study was a retrospective observational study conducted using the opt-out method. The study protocol was publicized extensively at Kumamoto University and the Kumamoto University website (http://www2.kuh.kumamoto-u.ac.jp/tyuokensabu/index.html), and patients were provided the opportunity to withdraw from the study.

Table 2. Time-Dependent Changes in Echocardiographic Findings After DLT in DLT Recipients (n=7)

	Pre-DLT period	Post-DLT period[A]	P value
IVST (mm)	10.6±1.9	11.5±1.6	0.15
PWT (mm)	9.8±1.5	11.6±1.7	<0.05
LVEF (%)	66.4±3.4	65.1±3.9	0.52
LAVI (mL/m^2)	39.9±15.3	48.0±29.6	0.25
E/A ratio	1.08±0.44	0.81±0.30	0.13
E' (cm/s)	7.2±2.6	6.0±1.8	0.32
E/e' ratio	13.3±5.3	10.3±1.9	0.18
TRV (m/s)	2.28±0.43	2.10±0.43	0.32
GLS (%)	−22.1±3.4	−16.9±2.3	<0.05
Apical LS (%)	−24.3±4.6	−21.0±4.3	0.24
Mid LS (%)	−22.7±4.3	−15.4±3.4	<0.05
Basal LS (%)	−19.3±4.4	−13.4±2.3	<0.05
RapLSI	0.58±0.08	0.75±0.20	<0.05
LVEF/GLS ratio	3.06±0.44	3.91±0.58	<0.05

[A]The mean period after DLT was 5.4 years. P values were obtained using paired t-tests. DLT, domino liver transplantation; E/A ratio, ratio between E- and A-wave velocity; E/e′ ratio, ratio between E-wave velocity and the early diastolic velocity of the septum at the level of the mitral annulus; GLS, global longitudinal strain; IVST, interventricular septum thickness; LAVI, left atrial volume index; LS, longitudinal strain; LVEF, left ventricular ejection fraction; PWT, posterior wall thickness; RapLSI, relative apical LS index; TRV, tricuspid regurgitation velocity.

Echocardiographic Measurements

TTE was performed in stable patients using Vivid 7 or Vivid E95 (GE Vingmed, Horten, Norway), Aplio XG (Toshiba, Tokyo, Japan), or Epiq 7 (Philips, Washington, DC, USA) ultrasound systems equipped with a 2.5-MHz phased-array transducer. Chamber size, wall thickness, and LV systolic function, represented by LV ejection fraction (LVEF), were evaluated using standard procedures.[11] LA volume index (LAVI), the ratio between E-wave velocity and A-wave velocity on pulsed-wave Doppler mitral flow imaging (E/A ratio), early diastolic velocity of the septum at the mitral annulus level (e' wave velocity) on tissue Doppler imaging, the E/e' ratio, and tricuspid regurgitation velocity (TRV) were calculated to quantify LV diastolic function.[12,13] STI was performed by another operator who was blinded to patients' clinical characteristics using vendor-independent software programs (2D Strain Analysis; TOMTEC Imaging Systems, Unterschleissheim, Germany) in patients with adequate endomyocardial border definition on TTE in the 4-, 3-, and 2-chamber apical views. Regional LS was determined in 16 segments of the LV in accordance with the American Society for Echocardiography guidelines.[11] Global LS (GLS) was calculated as the mean LS of these 16 segments. Apical LS was calculated as the mean LS of the apical 4 segments. Mid LS and basal LS were calculated as the mean LS of the mid 6 segments and basal 6 segments, respectively. The relative apical LS index (RapLSI; calculated as apical LS/[basal LS+mid LS]) and the ratio between LVEF and GLS were estimated as the hallmarks of CA on TTE.[9,10]

Statistical Analysis

Summary statistics as given as the mean±SD or number (percentage). Time-dependent changes in echocardiographic variables were analyzed using paired t-tests. Pearson's correlation coefficients were used to investigate associations between absolute changes in basal LS and observation years after DLT, as well as between basal LS and several factors, namely age at the time of DLT, age at the time of TTE, and observation years after DLT, with results shown using scatter plots. Patient clinical characteristics were compared between groups using Student's t-test or the Chi-squared test.

Independent variables associated with impaired basal LS were assessed using logistic regression analysis. The following variables were initially incorporated into the univariable logistic regression analysis model: age, male sex, hypertension, dyslipidemia, diabetes, smoking, dialysis, anticancer drug use, and history of DLT. Variables with P<0.10 were incorporated into the multivariable logistic regression analysis model. Intra- and interobserver variability for basal

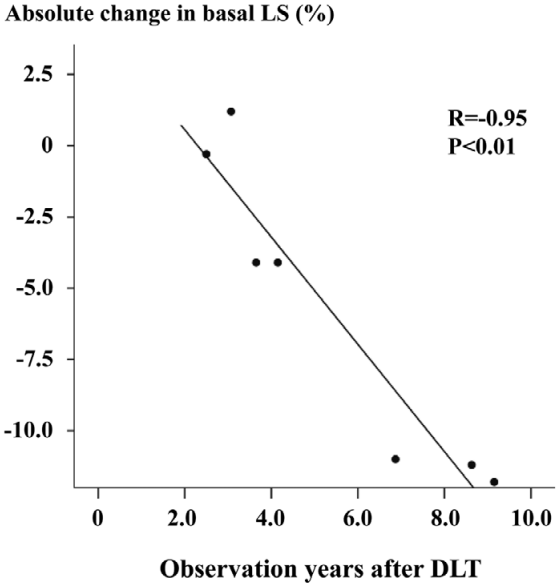

Figure 3. Correlation between absolute change in basal longitudinal strain (LS) and observation years after domino liver transplantation (DLT).

Table 3. Comparison Between the Impaired and Preserved Basal LS Groups Among DLT Recipients

	Impaired basal LS (n=7)	Preserved basal LS (n=7)	P value
Age (years)			
At time of DLT	57.2±3.5	39.6±16.0	<0.05
At time of TTE	65.4±5.6	48.3±13.3	<0.01
Observation after DLT (years)	8.2±4.2	8.7±4.1	0.82
Amyloid deposition in organs other than heart	4 (67)	5 (71)	0.85
Male sex	6 (86)	5 (71)	0.52
Hypertension	1 (14)	3 (43)	0.23
Dyslipidemia	1 (14)	1 (14)	1.00
Diabetes	3 (43)	1 (14)	0.24
Smoker	4 (57)	3 (43)	0.59
Dialysis	1 (14)	1 (14)	1.00
History of MI	0 (0)	0 (0)	1.00
Valvular diseases	1 (14)	0 (0)	0.30
Anticancer drugs	0 (0)	0 (0)	1.00

Unless indicated otherwise, data are given as the mean±SD or as n (%). P values were obtained using Student's t-test or the Chi-squared test. Abbreviations as in Tables 1,2.

LS was evaluated in 20 patients and assessed using intraclass correlation coefficients (ICCs).

All analyses were conducted using SPSS for Windows version 24.0 (SPSS Inc., Chicago, IL, USA). Statistical significance was set at 2-tailed P<0.05.

Results

Clinical Characteristics of the DLT Recipients

The clinical characteristics of the 14 DLT recipients (11 male, 3 female) enrolled in this study are given in **Table 1**. The mean age at the time of DLT was 48.3±13.9 years. Thirteen patients received domino liver grafts with the Val30Met mutation in the *TTR* gene, the most common type of *TTR* mutation worldwide, and only 1 patient received a graft with the Ser50Ile *TTR* mutation. The mean observation period after DLT was 8.4±1.0 years. Among the DLT recipients, 2 had received hemodialysis treatment, 1 had moderate aortic stenosis, none had myocardial infarction, and 2 required hospitalization because of heart failure. One patient who received the graft with the Ser50Ile *TTR* mutation was positive for technetium pyrophosphate (^{99m}Tc-PYP) amyloid deposition in the heart (^{99m}Tc-PYP visual grade 2) and died from a cardiovascular event 17 years after DLT. Another patient died from a non-cardiovascular event 11 years after DLT.

Time-Dependent Changes in Echocardiographic Findings in DLT Recipients

Time-dependent changes in echocardiographic findings after DLT were evaluated in 7 DLT recipients. All DLT recipients evaluated received domino liver grafts with the Val30Met *TTR* mutation. The mean observation period after DLT for these 7 recipients was 5.4±1.0 years. There were no significant differences in LVEF, E/A ratio, e' wave velocity, E/e' ratio, or TRV between the pre- and post-DLT periods (**Table 2**). In contrast, there were significant increases in GLS (−16.9±2.3 vs. −22.1±3.4; P<0.05), mid LS (−15.4±3.4 vs. −22.7±4.3; P<0.05), and basal LS (−13.4±2.3 vs. −19.3±4.4; P<0.05) in the post- vs. pre-DLT period. There were also significant increases in RapLSI (0.75±0.20 vs. 0.58±0.08; P<0.05) and the LVEF/GLS ratio (3.91±0.58 vs. 3.06±0.44; P<0.05) in the post- vs. pre-DLT period. The **Supplementary Figure** shows typical bullseye graphs of LS in DLT recipients (Patient No. 6 in **Table 1**) in the pre- and post-DLT periods. Absolute change in basal LS was significantly correlated with observation years after DLT (r=−0.95, P<0.01; **Figure 3**).

Clinical Characteristics in DLT Recipients vs. Control Subjects

The clinical characteristics of the DLT recipients and control subjects are given in the **Supplementary Table**. There were no significant differences in age at time of TTE and the proportion of men between the 2 groups. However, GLS (−17.1±2.1 vs. −19.4±2.1; P<0.01), basal LS (−14.7±3.8 vs. −17.8±2.2; P<0.05), and the LVEF/GLS ratio (3.87±0.50 vs. 3.35±0.43; P<0.01) were significantly higher in DLT recipients than in control subjects.

Comparisons Between DLT Recipients With Impaired and Preserved Basal LS

DLT recipients were divided into 2 groups based on the median basal LS value in the post-DLT period (−14%): the impaired basal LS group (>−14%) and the preserved basal LS group (≤−14%). Age at time of DLT (57.2±3.5 vs. 39.6±16.0 years; P<0.05) and TTE (65.4±5.6 vs. 48.3±13.3 years; P<0.01) was significantly higher in the impaired than preserved basal LS group (**Table 3**). There were no significant differences in other variables, including observation period after DLT and coronary risk factors, between the 2 groups. Age at the time of DLT and TTE was significantly correlated with basal LS in DLT recipients (r=0.75 [P<0.01] and r=0.80 [P<0.01], respectively; **Figure 4A**,**B**). In contrast, there was no significant correlation between age at the time of TTE and basal LS in control subjects (r=−0.53, P=0.05; **Figure 4C**). Although there was no correlation between observation years after DLT and basal LS across all DLT recipients (r=−0.06, P=0.83; **Figure 4D**), there was a significant correlation between observation years after DLT and basal LS after in the middle aged and elderly (age >45 years; r=0.69, P<0.05; **Figure 4E**).

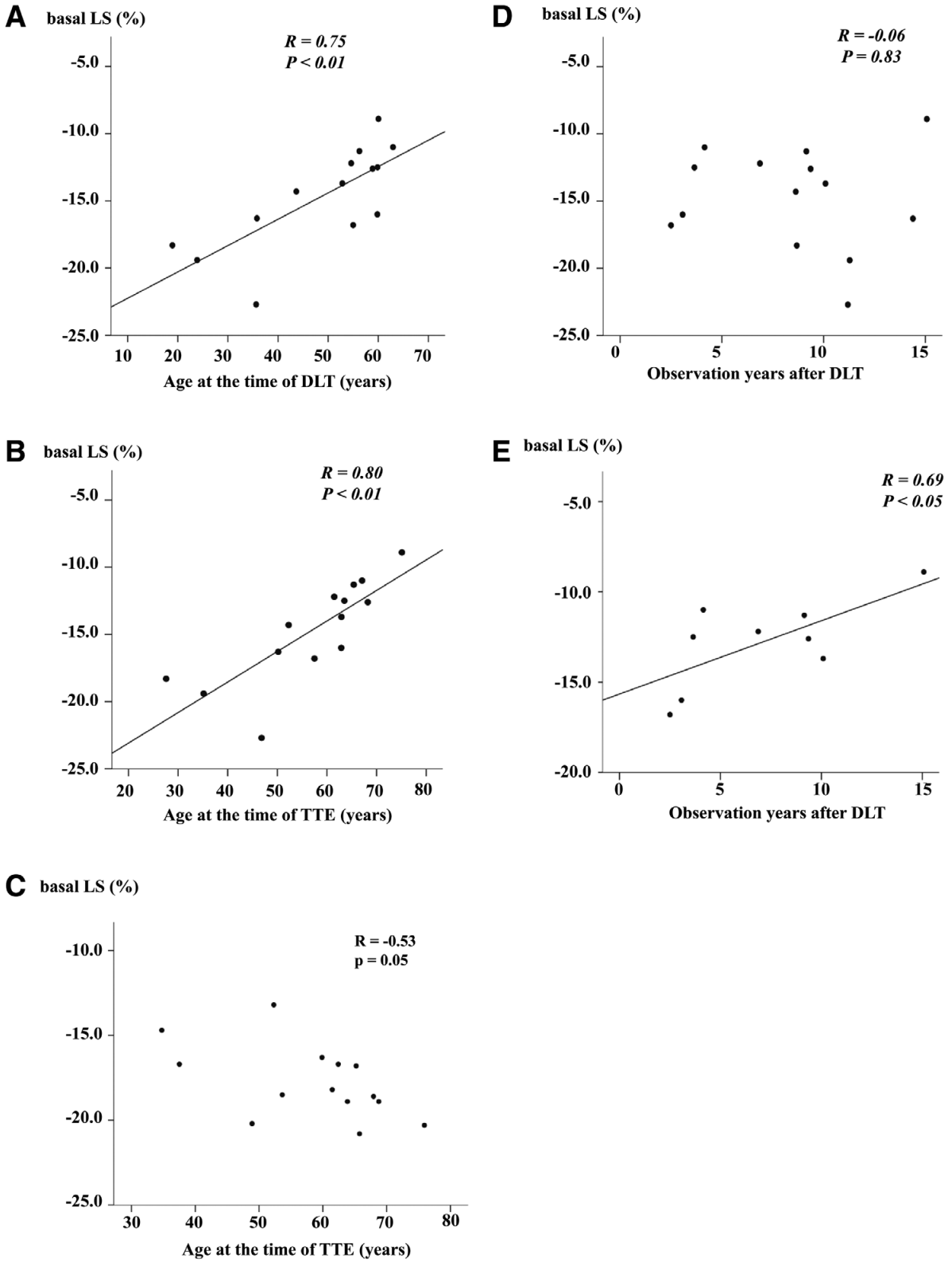

Figure 4. Correlations between basal longitudinal strain (LS) and different factors. (**A**,**B**) There were significantly correlations between basal LS and both age at domino liver transplantation (DLT; **A**) and age at transthoracic echocardiography (TTE; **B**). (**C**,**D**) There were no significant correlations between age at TTE and basal LS in control subjects (**C**) (or between observation years after DLT and basal LS in DLT recipients (**D**). (**E**) However, in middle aged and elderly DLT recipients (i.e., >45 years old), there was a significant correlation between observation years after DLT and basal LS.

Table 4. (A) Comparisons Between the Impaired and Preserved Basal LS Groups Among All Subjects (DLT Recipients and Controls), (B) Factors Associated With Impaired Basal LS Among All Subjects (DLT Recipients and Controls)

(A)	Impaired basal LS (n=8)	Preserved basal LS (n=20)	P value
Age at the time of TTE (years)	64.5±6.5	54.9±13.1	0.06
Male sex	7 (88)	15 (75)	0.47
History of DLT	7 (88)	7 (35)	<0.05
Hypertension	2 (25)	9 (45)	0.33
Dyslipidemia	1 (13)	5 (25)	0.47
Diabetes	3 (38)	2 (10)	0.09
Smoker	5 (63)	7 (35)	0.18
Dialysis	1 (13)	1 (5)	0.49
History of MI	0 (0)	0 (0)	1.00
Valvular diseases	1 (13)	0 (0)	0.11
Anticancer drug	1 (13)	3 (15)	0.86

(B)	Univariable analysis		Multivariable analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Age (per 1 year)	1.10 (0.99–1.23)	0.09	1.16 (0.99–1.34)	0.06
Male sex (+)	2.33 (0.23–23.91)	0.48		
Hypertension (+)	0.41 (0.07–2.53)	0.34		
Dyslipidemia (+)	0.43 (0.04–4.39)	0.48		
Diabetes (+)	5.40 (0.70–41.75)	0.11		
Smoker (+)	3.10 (0.57–16.96)	0.19		
Dialysis (+)	2.74 (0.15–49.53)	0.50		
Anticancer drug (+)	0.81 (0.07–9.17)	0.87		
History of DLT (+)	13.00 (1.32–128.11)	<0.05	28.39 (1.89–427.45)	<0.05

(A) Unless indicated otherwise, data are given as the mean±SD or as n (%). P values were obtained using Student' t-test or the Chi-squared test. (B) P values were obtained by logistic regression analysis. CI, confidence interval; OR, odds ratio. Other abbreviations as in Tables 1,2.

Comparisons in All Subjects (DLT Recipients and Controls) Between Those With Impaired and Preserved Basal LS

Using the same cut-off value for basal LS, all subjects (DLT recipients and controls) were divided into an impaired (>−14%) and preserved (≤−14%) basal LS group. The proportion of subjects with a history of DLT was significantly higher in the impaired than preserved basal LS group (88% vs. 35%; P<0.05; **Table 4A**). Multivariable logistic regression analysis revealed that a history of DLT was significantly associated with impaired basal LS in all subjects (odds ratio 28.39, 95% confidence interval [CI] 1.89–427.45, P<0.05; **Table 4B**).

Reproducibility

Analysis of intra- and interobserver variability for the 20 reassessed subjects showed good correlations for basal LS measurements (mean ICC 0.88 [95% CI 0.71–0.95%] and 0.93 [95% CI 0.82–0.97], respectively).

Discussion

The present study has several new findings. First, in many DLT recipients, cardiac systolic and diastolic function was preserved in the long term after DLT. Second, RapLSI and the LVEF/GLS ratio were increased in the post- compared with pre-DLT period. Third, the degree of impairment in basal LS was significantly correlated with the age at the time of DLT. Fourth, a history of DLT was significantly associated with impaired basal LS.

There are several reports about iatrogenic ATTR amyloidosis after DLT. However, many of these reports described TTR amyloid polyneuropathy. In contrast, there are only a few case reports on ATTR-CM after DLT.[5,6,14] Therefore, the time-dependent changes in cardiac function after DLT have not been fully clarified. The present study showed that LVEF, the E/A ratio, the E/e' ratio, e' wave velocity, LAVI, and TRV did not differ significantly between the pre- and post-DLT periods, indicating that LV systolic and diastolic function was preserved in the long term after DLT. Although previous studies reported that the period from transplantation to development of amyloid polyneuropathy in DLT recipients was shorter than expected,[15,16] cardiac function may be preserved in the long term after DLT. However, in the present study, 1 patient was positive for ^{99m}Tc-PYP amyloid deposition in the heart and died from a cardiovascular event. This patient received a graft with the Ser50Ile *TTR* mutation for DLT. We previously reported that non-Val30Met mutations were important risk factors for cardiovascular events in ATTRv patients.[17] Therefore, the DLT recipient who received a graft with the non-Val30Met mutation may have been at a higher risk of cardiovascular events than the other DLT recipients who received grafts with the Val30Met mutation.

RapLSI, a typical pattern of myocardial LS impairment, and the LVEF/GLS ratio can differentiate amyloid cardiomyopathy from other causes of LVH.[9,10] The present study showed that RapLSI and the LVEF/GLS ratio were both increased in the post- compared with pre-DLT period. However, in the post-DLT period, the mean LVEF/GLS ratio and RapLSI did not reach the cut-off values for a diagnosis of amyloid cardiomyopathy (cut-off values of 4.1

and 1.00, respectively) and many of the DLT recipients were negative for ^{99m}Tc-PYP. Gillmore et al[18] reported that combined findings of positive bone scintigraphy including ^{99m}Tc-PYP and negative monoclonal protein in the serum or urine had 100% specificity and positive predictive value for ATTR-CM in patients with suspected amyloid cardiomyopathy. Therefore, many DLT recipients in the present study were thought to have no obvious amyloid deposition in their heart in the post-DLT period. In contrast, this study showed that basal LS was impaired in the post-DLT period. Although impaired basal LS is a typical finding of amyloid cardiomyopathy,[19] various factors other than amyloid cardiomyopathy, such as coronary risk factors, chronic kidney disease, and anticancer drugs, affect basal LS.[20–22] However, any coronary risk factors, the history of dialysis and the use of anticancer drugs had no association with impaired basal LS in the present study. Aging was also associated with impaired basal LS.[23] However, there was no correlation between impaired basal LS and aging in the control subjects in the present study. In contrast, a history of DLT was significantly associated with impaired basal LS regardless of age. Therefore, impaired basal LS was thought to be caused by DLT, although many of the DLT recipients were negative for ^{99m}Tc-PYP. ^{99m}Tc-PYP is a useful modality to diagnose ATTR-CM. However, it cannot evaluate microscopic amyloid deposition in the heart. In contrast, LS can evaluate LV function accurately and is able to detect subtle regional and global LV dysfunction.[24] Thus, the increases in RapLSI and the LVEF/GLS ratio in the post- compared with pre-DLT period in DLT recipients who did not reach the cut-off values for a diagnosis of amyloid cardiomyopathy and impaired basal LS after DLT may indicate microscopic amyloid deposition in the heart that cannot be detected by ^{99m}Tc-PYP.

Interestingly, the present study clearly demonstrated that the degree of impaired basal LS was significantly correlated with age at the time of DLT, indicating that older DLT recipients have more amyloid deposition. Misumi et al[25] previously revealed that de novo amyloid deposition in areas other than the heart occurred earlier in older than younger DLT recipients. Consistent with that report, even in the heart, early amyloid deposition may occur in older DLT recipients. In general, age-related amyloid deposition can result from either the accelerated production or slowed clearance of amyloidogenic proteins. In the setting of TTR-related amyloidosis, reduced TTR clearance is presumably caused by aging because TTR production and serum concentrations decrease with aging.[26] The present study may suggest the importance of reduced TTR clearance with aging for amyloid deposition even in DLT recipients.

This study revealed that a history of DLT was a potential risk for subtle cardiac dysfunction. However, DLT procedures with liver grafts from ATTRv patients are critically required because of the severe shortage of liver grafts. Thus, periodic follow-up by TTE may be important for these patients. Moreover, investigation of the precise clinical course of acquired ATTR-CM is necessary. Maurer et al[27] reported the usefulness of tafamidis meglumine, a TTR stabilizer, for the treatment of ATTR-CM; as such, the usefulness of tafamidis meglumine for patients after DLT should be evaluated.

The present study had several limitations. First, the study was a single-center study. Thus, we were only able to evaluate time-dependent changes in echocardiographic measurements for 7 DLT recipients. Consequently, there may be a bias related to the sample size. Validation using a similar cohort would be useful to support our results, but is not possible because there have only been case reports on cardiac function after DLT. Therefore, despite the small number of subjects, we believe that our results have significant value. Second, we did not evaluate cardiac magnetic resonance imaging (CMR) in this study. CMR is an important imaging modality because of its high diagnostic performance for ATTR-CM. However, we were unable to evaluate CMR because many of the patients had no typical conventional echocardiographic findings of ATTR-CM and the cost of CMR is high. Third, we randomly enrolled control subjects after matching them with DLT recipients for age and sex. Thus, there were several differences (other than age and sex) between the DLT recipients and controls, such as morbidity rates of diabetes, dialysis, and malignancy, and these may have affected the findings of the present study. Despite these limitations, the present study is the first to demonstrate preserved LV systolic and diastolic function in the long term after DLT and subtle cardiac impairment evaluated by 2D STI in DLT recipients.

Conclusions

LV systolic and diastolic function was relatively preserved in the long term after DLT. However, 2D STI revealed subtle cardiac dysfunction in DLT recipients, which may be an early expression of cardiac amyloidosis.

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Disclosures

K.K., K.T. are members of *Circulation Reports*' Editorial Team.

IRB Information

This study was approved by the institutional review board and ethics committee of Kumamoto University (Reference no. 1588).

Data Availability

The deidentified participant data will not be shared.

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Supplementary Files

Please find supplementary file(s);
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