Box 2 Exclusion criteria

- Patients with an implantable device (ie, pacemaker, implantable cardioverter defibrillator), because an alternating-current signal travels through the body when the patients measure their body weight and body fat using an electronic scale.
- Undergoing dialysis or serum creatine level ≥3.0 mg/dl.
- Severe liver dysfunction.
- Planned percutaneous coronary intervention or coronary artery bypass grafting.
- Unable to stand on a scale safely.
- Limited life expectancy (malignancy or other cause).
- Severe depression (eg, Patient Health Questionnaire score ≥20).
- Severe dementia.
- Pregnancy.
- Without access to a telephone line.

expectancy due to malignancy or other cause; patients in whom severe depression is highly suspected (eg, PHQ-9≥20); patients with severe dementia; in pregnancy; and patients without access to a telephone line (box 2). Patients suspected of having mild-to-moderate depression (eg, PHQ score: 5–19) are recommended to receive adequate intervention from a psychiatrist or clinical psychologist.

Study design

The Home Telemonitoring Study for Japanese Patients with Heart Failure (HOMES-HF) is a multicentre, prospective RCT, funded by the Japanese Ministry of Health, Labor and Welfare (Clinical Trials registration number UMIN000006839; http://www.umin.ac.jp/ctr/index.htm) and conducted to compare automated physiological data monitoring with usual care. Written informed consent will be obtained by the patient's physician prior to discharge or within 30 days of hospital discharge after admission for acute HF or acute exacerbation of HF. Eligible patients are randomly assigned via a website to either the telemonitoring group or the usual care group by using a minimisation method with biased-coin assignment balancing on age (≥65 vs <65 years), left-ventricular ejection fraction (LVEF) (≥30% vs <30%), and having a history of ischaemic heart disease (IHD; IHD vs non-IHD). The patients and treating physicians are not masked to the treatments, while assessment of the outcome is masked. According to the study protocol, participants will be enrolled until August 2013 and followed until August 2014.

Endpoints

The primary endpoint is a composite of all-cause death and rehospitalisation due to worsening HF. The secondary endpoints are: all-cause death; cardiac death; all-cause rehospitalisation; rehospitalisation due to a cardiovascular cause; rehospitalisation due to worsening HF; worsening of symptoms; cost of medical care; worsening of LVEF or the levels of N-terminal pro B-type natriuretic peptide, high-sensitivity C reactive protein, pentraxin-3 (PTX3), high-sensitivity cardiac troponin T or high-molecular weight adiponectin; changes in the Mini Mental State Examination (MMSE) score, the General Self Efficacy Scale (GSES), the Minnesota Living With Heart Failure (MLWHF) score or the PHQ-9 score and adherence to medication.

Telemonitoring system

The telemonitoring system of the HOMES-HF study consists of an electronic scale, a sphygmomanometer and a device that receives acquired physiological data (blood pressure, pulse rate and body weight) wirelessly and transmits the data to the central web server via the internet. It is commercially available as a health-maintenance product (Karada Karte Tanita health-link Co. Ltd, Tokyo, Japan). These devices are distributed to the participants assigned to the telemonitoring group when they are discharged from the hospital. Patients' physicians encourage the participants assigned to the telemonitoring group, when they demonstrate how to use the monitoring devices after obtaining the informed consent, to measure their body weight and blood pressure by themselves at least once a day at approximately the same time in order to minimise daily variance caused by meals, micturition and bowel movement. The acquired physiological data are automatically transmitted to a central web server immediately after measurement. The telemonitoring centre was newly established at Saga University for the present study, and full-time nurses monitor the acquired data on the secure website 7 days a week (see online supplementary appendix 1). At first contact with the participant by telephone, the monitoring nurses establish communication connection between the monitoring devices and the central web server and arrange a time zone convenient to the participant for regular measuring. Before telemonitoring is started, the patient's physician determines an acceptable range of body weight, blood pressure and pulse rate for each patient and makes a declaration of these ranges to the telemonitoring centre. If the body weight, blood pressure or heart rate would exceed the acceptable range, the monitoring nurses serve a notice to the patient's physician. There are no restrictions on the ability of the patient's physician to perform any interventions in response to the notice, such as providing telephone guidance, changing or adding medications and ordering hospital readmission, with the exception that the physician must provide feedback regarding their interventions to the telemonitoing centre. The patient's physician assumes responsibility for acting on the information.

Introducing the concept of PCC into the telemonitoring system to encourage adherence in participants

After hospital discharge, the patients and their family, especially among elderly persons, have a tendency to be

socially isolated, and that makes it difficult to practice self-management. In order to motivate the patients assigned to the telemonitoring group to maintain adherence to daily measurement of their body weight and blood pressure, the concept of PCC was proactively introduced into the telemonitoring system for the HOMES-HF study. Enhanced clinician–patient communication, patient empowerment and self-management are the elements of PCC.[22 23] To this end, professionals (typically nurses, although sometimes the patients' physicians) provide advice and education to the patients assigned to the telemonitoring group and create a care plan until the next visit referring to the patients' electronic health records acquired by daily monitoring on the website using a tablet computer in collaboration with the patients at every visit of theirs to the outpatient clinic. According to the protocol, the patients' physicians or nurses have to report to the monitoring centre what they performed for the patient according to the notice from the monitoring nurses. Moreover, we designed the monitoring system to be accessible to the patients' family in order for them to watch over their parents, spouse, siblings or relatives. In this way, we intend to enable the patients to recognise that all healthcare professionals around them and their family are not only monitoring on the website, but also communicating with each other. We believe that these efforts may help reassure patients and their family, as well as encourage them to participate in decision-making on their own treatment by collaborating with healthcare professionals and improve adherence to medical treatment.

Usual care

Patients assigned to the usual care group are treated by their physician in accordance with the Japanese Circulation Society Guidelines for treatment of chronic HF 2010. Clinicians provide discharge education and encourage the patients to measure their body weight by themselves every day.

Sample size calculation

We assumed that the HR of the primary endpoint (all-cause death and hospitalisation for worsening HF) of the telemonitoring group to the control group would be 0.60 and that the cumulative annual event rate in the usual care group would be 0.30, based on the result of previous studies.[10 13] This trial is designed to have 80% power to detect a 40% relative reduction in the risk of the primary outcome in the telemonitoring group within 12 months, as compared with the control group, based on an expected death rate at 12 months of 30% in the control group using a log-rank test with a two-sided α of 0·05. A total sample size of 420 patients is planned according to the Schoenfeld and Richter method,[24] with a 2-year period for patient enrolment and a follow-up period of 1 year.

Statistical analysis

All statistical analyses will be independently performed at the Chiba University Hospital Clinical Research Center (see online supplementary appendix 2). The analyses of the adjudicated primary and secondary outcomes will be conducted using data for all patients who had undergone randomisation, according to the intention-to-treat principle. For the baseline variables, summary statistics will be constructed employing frequencies and proportions for categorical data and means and SD for continuous variables. The patient characteristics will be compared using Fisher's exact test for categorical outcomes and t tests for continuous variables, as appropriate. The primary endpoint of a composite of all-cause death and rehospitalisation for worsening HF will be analysed using the stratified log-rank test for eligible patients with age (≥65 vs <65 years), LVEF (≥30% vs <30%) and history of ischaemic heart disease (IHD vs non-IHD) as stratification factors. Time to events will be estimated using the Kaplan-Meier method, and HRs and 95% CIs will be calculated using the Cox proportional hazards models with stratification factors. Sensitivity analyses will also be performed by means of the unadjusted Cox models.

All comparisons are planned, and all p values will be two-sided. A p value of less than 0.05 will be considered to be statistically significant. All statistical analyses will be performed using SAS software V.9.3 (SAS Institute, Cary, North Carolina, USA).

Data collection schedule

At the time each patient is enrolled into the study, investigators at each local site (see online supplementary appendix 6) perform a baseline history and physical examination and conduct a survey of the baseline scores of three types of questionnaires (PHQ-9, MMSE and GSES). The outcomes are assessed at 6 and 12 months after enrolment into the study. Clinicians at each local site submit a report to the data centre at these time points to assess psychosocial status, self-care skills, quality of life and rehospitalisations. We will evaluate the cost-effectiveness of the telemonitoring interventions, incorporating the costs associated with hospitalisations, outpatient visits, emergency department visits and home care services.

Study management

Data on the primary and secondary endpoints and adverse events are collected when the events occur. All data are collected by the independent data management centre established for the present study at the Chiba University Hospital Clinical Research Center (see online supplementary appendix 2). There will be no direct communication between HOMES-HF investigators and the Coordinating Data Center. The clinical data entry (double data entry), cording, data management and reporting will be performed by a data management system, HITCANDIS/DM (HITachi Computer Assisted

New Drug Information System/Data Management for clinical trial, Hitachi, Ltd Tokyo, Japan). Trained coding specialists will code the clinical data using standard coding dictionaries including MedDRA for adverse events and medical history and considering WHO-DD for concomitant medications. All the data management processes are tracked electronically, allowing regular updates on patient status, data receipt including missing segments or pages, data entry and verification, data query status and protocol deviations. In order to ensure consistency, integrity and accuracy for this study, these processes are based on the standard operating procedures.

An independent endpoint committee (see online supplementary appendix 3) consisting of three members, who are blinded to any information relating to the group allocations, evaluates each event and classifies the results. An independent data and safety monitoring board (see online supplementary appendix 4) composed of three members reviews all reports from the endpoint committee to advise early termination of the study for safety, scientific or ethical reasons. A steering committee (see online supplementary appendix 5) is responsible for the study design and scientific execution of the study.

Laboratory measurements

The plasma PTX3 levels are measured with a sandwich ELISA kit (Perseus Proteomics Inc, Tokyo, Japan) based on a previously described method.[25] The plasma HMW-adiponectin levels are measured using a sandwich ELISA kit (Fujirebio, Tokyo, Japan) based on a monoclonal antibody to human HMW-adiponectin, IH7.[26]

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Competing interests All authors have completed the ICMJE form for disclosure of potential conflicts of interest at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that NK is currently an endowed chair from Fukuda Denshi Co., Ltd, which is a medical equipment manufacturer. The company has no relation to the monitoring equipment used in this study. All authors have no other relationships or activities that could appear to have influenced the submitted work.

Ethics approval All participants will provide their written informed consent, and the study protocol has been approved by the institutional review board of Saga University and each participating site.

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Home telemonitoring study for Japanese patients with heart failure (HOMES-HF): protocol for a multicentre randomised controlled trial

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ORIGINAL ARTICLE

Interrelation between myocardial oxidative metabolism and diastolic function in patients undergoing surgical ventricular reconstruction

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Abstract
Purpose Diastolic function is impaired in patients with end-stage heart failure. Favorable structural changes by surgical ventricular reconstruction (SVR) are thought to improve diastolic function, however, previous studies reported the contradictory results. We hypothesized that cardiac oxidative metabolism and diastolic dysfunction might improve in parallel to the reduction of left ventricular chamber size after SVR.
Methods We studied 11 patients underwent SVR associated with mitral valve repair for end-stage heart failure due to dilated cardiomyopathy. Diastolic function was assessed by echocardiography and myocardial oxidative metabolism was measured by the monoexponential clearance (k-mono) of ^{11}C-acetate positron emission tomography at baseline and 1 month after SVR.
Results All patients had preoperative severe diastolic dysfunction [E/A 4.11±1.18, deceleration time (DT) 134± 26 ms]. The study patients were divided into 2 groups according to the changes in diastolic function after SVR; unchanged or worsened diastolic function in 6 patients (55 %, Non-responder) and improved diastolic function in 5 (45 %, Responder). K-mono and wall stress decreased only in responder. The changes in k-mono before and after SVR correlated with those in deceleration time (r= –0.63; p< 0.05) and wall stress (r=0.75; p<0.01).
Conclusions Improvement of diastolic dysfunction in patients with end-stage heart failure by SVR was in parallel to that in oxidative metabolism. It suggests that SVR reduced excessive metabolism during the diastolic phase, in part, via the improvement in diastolic function and the reduction in LV wall stress.

Keywords Diastolic function · Heart failure · Oxidative metabolism · Wall stress · Surgical ventricular reconstruction

Introduction

Not only systolic function but also diastolic function is severely impaired in patients with end-stage heart failure. The observational cohorts in heart failure patients with and without diastolic dysfunction show that the effects of diastolic dysfunction on cardiac death are as high as those of systolic dysfunction [1]. Surgical ventricular reconstruction (SVR) modifies spherical left ventricle (LV) shape into elliptical one and reduces chamber size and wall stress in left ventricle [2]. Although the appropriate morphological changes in LV by SVR are thought to improve LV diastolic function, previous clinical studies show the controversy about the effect of SVR [3]. The heterogeneous results are due to the complexity of etiologies of restrictive LV (LV wall stiffness and stress). For example, LV wall stiffness in patients with severely dilated LV is associated with massive scar burden and loss of viable myocardium. Elevated LV

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wall stress is associated with large LV dimension, spherical shape, and volume overload with mitral regurgitation. Thus, SVR could improve the latter, but not the former. Another reason for the controversy may be the lack of information about the effects of SVR on myocardial metabolism in patients with restrictive LV. Beta-blocker therapy and cardiac resynchronized therapy can improve cardiac metabolism [4, 5]. If the reduction of LV chamber size is also effective on myocardial metabolism as well as LV diastolic function, these variables would change in parallel after SVR. We, thus, test the hypothesis that cardiac oxidative metabolism will decrease in patients whose diastolic dysfunction improve after SVR and that its potential mechanism may be the reduction of excessive energy loss during LV relaxation due to the improvement in diastolic dysfunction.

Material and methods

Study patients

Forty-one patients with end-stage HF undergoing overlapping left ventriculoplasty (OLVP) in our institution between June 2006 and January 2012 were prospectively enrolled in the study (Fig. 1). Nineteen had incomplete data acquisition (6 mechanical support before and/or after OLVP, 4 death, 1 incomplete echocardiography data, and 8 not consent to have a test). Eleven patients without severe diastolic dysfunction were excluded. Thus, the study population consisted of 11 patients with severe diastolic dysfunction. The

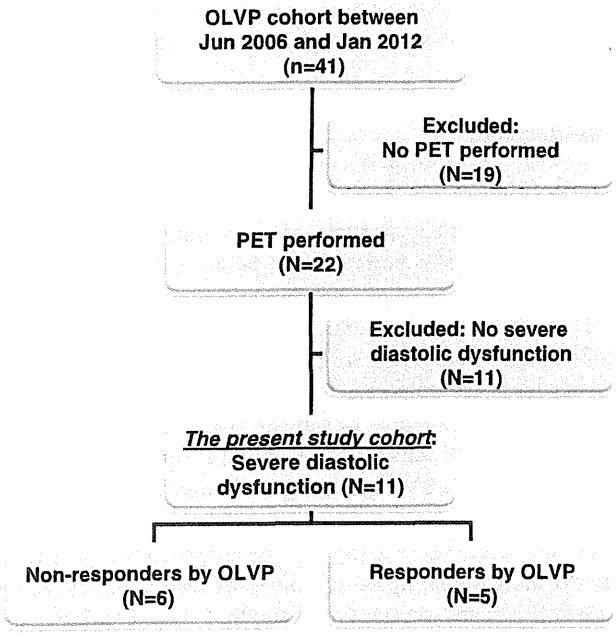

Fig. 1 Flow chart of the SVR study cohort

study was approved by the institutional ethical committee and the procedures were in accordance with institutional guidelines. Informed consent was obtained from each study patient.

Surgical techniques

We performed OLVP and its technique has been described previously in detail [6, 7]. It was combined with mitral complex reconstruction (MCR) [7], which included MV repair, such as papillary muscle approximation (PMA), papillary muscle suspension (PMS), and mitral annuloplasty (MAP) in the presence of mitral regurgitation (MR).

Study protocol

Echocardiographic assessment and ^{11}C-acetate PET were performed before and after the surgical procedures. Echocardiography and ^{11}C-acetate PET was repeated in all patients (33 ± 10 days) after OLVP. All patients had MV repair (MAP in 11, PMA in 10, and PMS in 10) with OLVP. Six out of 11 patients had concomitant coronary artery bypass grafting.

Echocardiography

Echocardiographic examination (Artida ultrasound system, Toshiba Medical Systems) was performed by experienced sonographers and experienced cardiologists. Left ventricular end-diastolic dimension (LVDd), Left ventricular end-systolic dimension (LVDs), end-diastolic posterior wall thickness (LVPWD), end-systolic posterior wall thickness (LVPWS) were measured. Left ventricular mean wall stress (WS) was calculated according to following formula: [8]

$$WS = \text{systolic blood pressure} \times [(LVDd + LVDs)/2 \times (LVPWD + LVPWS)]$$

LV end-diastolic volume (EDV), end-systolic volume (ESV), and EF were measured from apical 2-chamber and 4-chamber views using the biplane method of disks. The LV shape was characterized by means of the sphericity index (SI), which is the ratio of the short axis to the long axis, and was calculated in systole and diastole [9].

Mitral regurgitation (MR) was classified as none (grade 0), mild (grade 1), moderate (grade 2), moderately severe (grade 3), and severe (grade 4) according to the AHA guideline [10]. The Doppler sample volume was placed at the tip of mitral valve leaflets, and a pulsed-wave Doppler recording was obtained. Early (E) and late (A) transmitral velocity as well as the deceleration time (DT) were measured and the early/late transmitral diastolic peak flow velocity (E/A) ratio was also calculated [11]. An echocardiographic assessment of LV diastolic function was classified into 4 categories: normal,

impaired relaxation, pseudo-normal, and restrictive filling pattern (RFP: severe diastolic dysfunction) [12–14].

After surgery, diastolic function was defined as improved (at least one class less), unchanged (no difference in diastolic pattern), or worsened (E/A ratio increase of at least 20 %) [15]. Patients with preoperative RFP were divided into two groups: patients with unchanged or worsened diastolic function (Non-responder) and patients with improved diastolic function (Responder) after OLVP. Definition of responder was based on the improvement of echocardiographic restrictive filling pattern after OLVP. Accordingly, E/A<2 and DT>140 ms were considered as responder. Definition of non-responder was based on the persistence of restrictive filling pattern defined as E/A>=2 or 0.75<E/A<2 plus DT<=140 ms after OLVP. This cut-off value was chosen from the previous studies by Bursi et al [14]. and Pozzoli et al [16].

Forward stroke volume (FSV) was derived from the velocity-time integral of the pulsed Doppler LV outflow tract velocity signal and the LV outflow tract diameter [7]. Forward stroke volume index (FSVI) was derived by dividing FSV by the body surface area (BSA). Cardiac output was calculated according to following formula: echocardiographic cardiac output = FSV × heart rate.

^{11}C-acetate PET

PET was performed using a whole-body scanner (ECAT/EXACT HR+; Siemens/CTI, Knoxville, TN, USA). 740 MBq of ^{11}C-acetate was administered intravenously for 60 s under resting conditions. Dynamic PET acquisition was performed (10×10 s, 1×60 s, 5×100 s, 3×180 s, 2×300 s) [17]. PET data analysis was performed using the dedicated software [17]. The images were iteratively reconstructed and were resliced along the short axis. Blood pressure and heart rate were monitored during PET scan to calculate a rate-pressure product. A mono-exponential function was fit to the myocardial time activity data, and the clearance rate constant (k-mono) was determined as described previously [7, 17]. Myocardial blood flow (MBF) was also calculated from ^{11}C-acetate PET data [18].

Myocardial efficiency

Myocardial efficiency (Work Metabolic Index) was assessed by effective (forward) work divided by myocardial oxygen consumption as follows; [4]

$$[\text{Systolic blood pressure} \times \text{heart rate} \times \text{FSV}] \div \text{BSA} \div \text{k-mono}.$$

We also computed another Work Metabolic Index to count for LV mass; [19]

$$\text{WMI}_{\text{LVM}} = (\text{Mean blood pressure} \times \text{heart rate} \times \text{FSV})/(\text{k-mono} \times \text{LV mass}).$$

Statistical analysis

Data are expressed as mean ± standard deviation or percentages of patients. Differences were compared by Wilcoxon non-parametric test for Gaussian variable. The ratio between baseline and after OLVP was compared by χ^2 test. $P<0.05$ was considered significant for all tests.

Results

Patient characteristics

Clinical characteristics, hemodynamics, and echocardiographic data are summarized in Tables 1 and 2. Mean age was 59 years and all were male. Mean NYHA functional class was 3.1 (91 % was class III or IV) and mean ejection fraction was 26 %. Etiologies of heart failure were ischemic in 6 patients and

Table 1 Patient characteristics

Variables	n=11
Age (years)	59±8
Male, n (%)	11 (100)
BSA (m^2)	1.7±0.1
BMI (kg/m^2)	23±3
Etiologies of heart failure	
Ischemic, n (%)	6 (55)
Non-ischemic, n (%)	5 (45)
Hypertension, n (%)	2 (18)
Diabetes mellitus, n (%)	5 (45)
Dyslipidemia, n (%)	6 (55)
Smoking, n (%)	10 (91)
Medications	
ACEI/ARB, n (%)	8 (73)
Beta blocker, n (%)	9 (82)
Diuretics, n (%)	11 (100)
Spironolactone, n (%)	7 (64)
Digitalis, n (%)	2 (18)
Nitrate, n (%)	4 (36)
Amiodarone, n (%)	2 (18)
Dobutamine, n (%)	1 (9)
Carperitide, n (%)	1 (9)
Device implantation	
CRT-D, n (%)	1 (9)

BSA body surface area, *BMI* body mass index, *ACEI* ACE inhibitor, *ARB* angiotensin-receptor blocker, *CRT-D* cardiac resynchronization therapy with defibrillator

Table 2 Effects of OLVP on NYHA functional class, hemodynamic parameters, echocardiographic parameters, and oxidative metabolism

	Baseline	After OLVP	P
NYHA	3.1±0.5	1.5±0.5	<0.001
NYHA 3 or 4, n (%)	10 (91)	0 (0)	<0.001
Hemodynamic parameters			
HR (/min)	70±12	84±14	<0.01
SBP (mmHg)	99±20	101±15	0.71
Echocardiographic parameters			
EDV (mL)	324±93	201±70	<0.01
ESV (mL)	241±71	160±72	<0.01
EF (%)	26.0±6.6	30.3±5.7	0.14
FSVI (ml/m^2)	26.9±9.7	31.8±10.6	0.08
MR grade	3.3±0.9	0.3±0.5	<0.001
PASP (mmHg)	55.2±8.4	45.9±12.7	0.06
IVC (mm)	18.6±3.4	17.3±3.9	0.31
E/A	4.11±1.18	2.87±1.16	0.09
DT (ms)	134±26	179±35	<0.05
WS (g/cm^2)	316±91	277±66	<0.05
LAD (mm)	59.2±7.6	56.4±6.8	<0.01
SI systole	0.61±0.13	0.62±0.13	0.63
PET measures			
k-mono (/min)	0.049±0.006	0.048±0.006	0.97
MBF (mL/g/min)	0.57±0.76	0.60±0.22	1.00
WMI×10^6 (mmHg· mL/m^2)	3.90±1.47	5.58±1.88	<0.01
WMI$_{LVM}$×10^3 (mmHg· mL· g^{-1})	12.2±4.6	19.5±7.3	<0.01

NYHA New York heart association functional class, *SBP* systemic blood pressure, *HR* heart rate, *EDV* end-diastolic volume, *ESV* end-systolic volume, *EF* ejection fraction, *FSVI* forward stroke volume index, *MR* mitral regurgitation, *PASP* pulmonary artery systolic pressure, *IVC* inferior vena cava diameter, *LAD* left atrial diameter, *SI* sphericity index, *WS* LV mean wall stress, *E/A* early/late transmitral diastolic peak flow velocity ratio, *DT* deceleration time of E wave, k-mono: myocardial clearance rate constant, *MBF* myocardial blood flow, *WMI* work metabolic index

non-ischemic in 5 patients. All patients received the standard pharmacological treatment including ACE inhibitors, angiotensin receptor blockers, and diuretics.

Effects of OLVP

The effects of OLVP on clinical variables are shown in Table 2. The improvement in NYHA functional class was observed in all patients ($p<0.001$). The prevalence of patients in NYHA functional class III–IV decreased from 91 % to 0 %.

OLVP significantly decreased ESV ($p<0.01$) and LV wall stress ($p<0.05$). ESV did not dilate from 1 month to chronic phase between 6 months and 12 months after OLVP [ESV 175± 89 mL to 119±26 mL; $p=0.25$, $n=5$]. Cardiac output significantly increased from 3.1±0.9 to 4.2±1.5 L/min·m^2 after OLVP ($p<0.01$). LV ejection function slightly increased, which, however, did not reach statistical significance. Severe mitral regurgitation disappeared. The change in E/A was only modest. DT significantly prolonged by 34 % ($p<0.05$). FSV index tended to increase while k-mono did not change ($p=0.97$), which was associated with increase in work metabolic index ($p<0.01$). MBF did not change after operation ($p=1.00$).

When we compared the changes in clinical variables between patients with ($n=11$) and without ($n=11$) severe diastolic dysfunction, there were no significant variables between groups. We further determined the effects of OLVP on echocardiographic diastolic parameters. The study was divided into two groups according to the diastolic function at 1 month after SVR: 6 patients (55 %) with unchanged (36 %) or worsened (18 %) diastolic function (Non-responder) and 5 (45 %) with improved diastolic function (Responder) after OLVP. Etiologies of heart failure was ischemic ($n=4$) and non-ischemic ($n=2$) for non-responder, and ischemic ($n=2$) and non-ischemic ($n=3$) for responder.

Only MBF was significantly higher in responder than in non-responder (1.23±0.98 mL/g/min vs 0.42±0.11 mL/g/min, $p<0.05$) among baseline parameters. There were no differences in preoperative k-mono, EDV, ESV, MR grade, FSVI, LVEF, WMI, NYHA, E/A, DT, LV wall stress, and sphericity index between the two groups. After OLVP, ESV was significantly decreased ($p<0.01$) and the degree of changes (delta ESV: −80 mL) was similar between 2 groups (Fig. 2a). As expected, the increase in DT was significantly greater in responders than non-responders (74.2±23.5 versus 19.7±44.4; $p<0.05$)(Fig. 2c). The changes in LV wall stress (ΔWS) in responders was greater than non-responders (Fig. 2d) as did that in k-mono (Δk-mono) (Fig. 2e). Work metabolic index increased in both groups (Fig. 2f). The changes in WMI and WMI$_{LVM}$ were not significantly different between responder and non-responder.

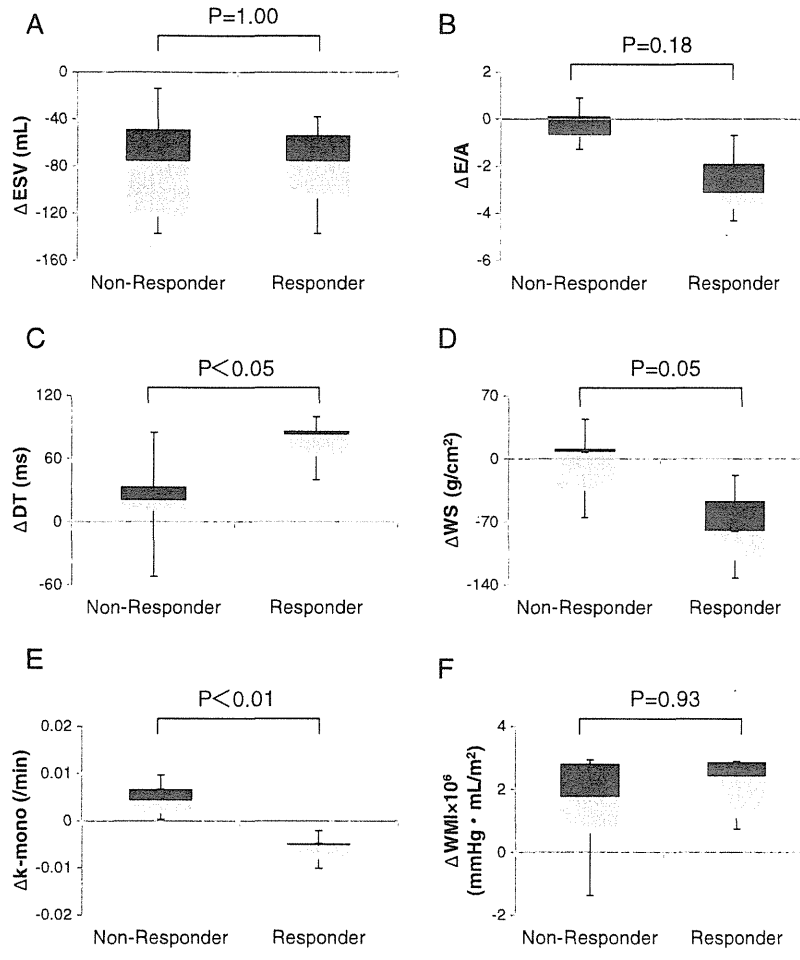

Fig. 2 Comparison of non-responders (n=6) versus responders (n=5) in the changes from baseline to postoperative data. **a** End-systolic volume (ESV), **b** E/A, **c** Deceleration time (DT), **d** LV wall stress (WS), **e** k-mono, **f** Work metabolic index (WMI)

Regarding outcome, four patients of 11 (36 %) died in all patients with severe diastolic dysfunction. One of 5 (20 %) died in responder, and 3 of 6 (50 %) died in non-responder, during the follow up (1,391±1,180 days).

Univariate regression analysis confirmed the changes in LV wall stress (ΔWS) after OLVP negatively correlated with those in DT (ΔDT) (r=–0.65, P<0.05). Likewise, the significant relationship was observed between Δk-mono and ΔDT (Fig. 3a) or ΔWS (Fig. 3b). ΔDT positively correlated with ΔFSVI (r=0.71, p< 0.05). ΔCardiac output by OLVP did not correlate with Δk-mono (r=0.085, p=NS). Likewise, ΔLVEF and ΔFSVI did not correlate with Δk-mono (r=0.033, p=NS and r=–0.37, p=NS, respectively). ΔMBF did not correlate with delta in any parameters.

Discussion

The present study demonstrated that a half of patients with severe dilated cardiomyopathy were responders for OLVP in terms of diastolic function. In these responders, oxidative metabolism significantly decreased, suggesting the interrelation between cardiac metabolism and diastolic function in heart failure.

Effects of SVR on diastolic function

In patients with severe dilated cardiomyopathy, decreased LV compliance is common and has been shown to be associated with symptoms and outcomes [12]. E/A and DT, reflecting diastolic function, are more sensitive to evaluate these abnormalities than systolic function in this population [20]. Our data demonstrated that a half of patients had improvement in DT and E/A after OLVP, suggesting that these patients were thought to be responders of intensive surgical treatment. The proportion of responders by SVR in diastolic dysfunction is consistent with the prior studies [15]. However, there are some advantages in our OLVP in combination with MCR. Unlike Dor and SAVE procedures, no use of patches in our OLVP procedure may have an advantage for improvement in diastolic function. LV diastolic function is impaired after tetralogy of Fallot repair probably due to the use of ventricular septal defect patch [21] and that surgical anterior ventricular restoration with stiff patch increased the LV stiffness compared to no use of patch in the dilated LV [22]. These studies support the superiority of our procedural concept. In addition, MCR could

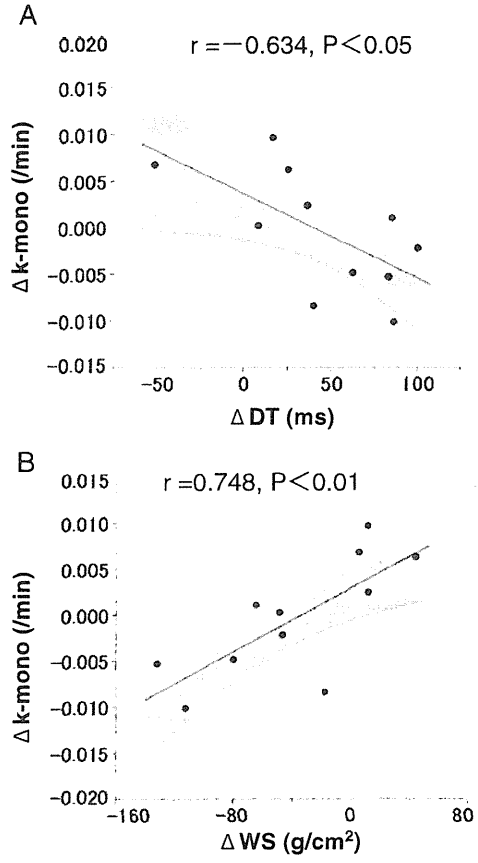

Fig. 3 Correlation between Δk-mono and ΔDT (**a**) or ΔWS (**b**)

prevent LV from remodeling because this procedure theoretically shortens circumferential LV dilation and reduces volume overload by correction of mitral regurgitation [23, 24]. In fact, the previous study and ours demonstrated that adequate reduction of LV volume is associated the improvement in heart failure symptom and outcome [25].

Interaction between diastolic function and myocardial oxygen metabolism

There is little information about the interrelation between diastolic function and cardiac metabolism except the study by Meyer et.al showing that elevated LV stiffness is correlated with peak oxygen consumption [26]. Although LV oxidative metabolism is reduced in advanced heart failure with extensive scar myocardium [27], the present study further demonstrated that the oxidative metabolism could be influenced by OLVP in patients with severe diastolic dysfunction and that the metabolic changes was observed in parallel with the changes in wall stress and diastolic function. The studies by Meyer et al and ours suggest that diastolic dysfunction may be the potential determinant of oxidative metabolism in addition to heart rate, wall stress, and contractility [28]. However, the changes in systolic function by OLVP did not correlate with those in LV oxidative metabolism, rather wall stress had a greater effect on LV oxidative metabolism only in responder. 91 % of patients, which had moderate to severe MR had been treated with MV surgery in this study. Chow et.al reported MV surgery did not change k-mono [29], because MR loaded a volume, but not a pressure. Some explanation that diastolic dysfunction is associated with increasing cardiac metabolism might be provided. In histopathologic studies, sarcomere loss and myocardial fibrosis were observed in the segments with dysfunctional but viable myocardium. The presence of sarcomere loss and fibrosis prevent functional recovery after revascularization [30]. In fact, non-responders in terms of diastolic function had no changes in oxidative metabolism. Other factor which influences metabolism is LV wall stress. This is also demonstrated in the present study that wall stress tended to decrease and k-mono significantly decreased in responders, but not in non-responders. Although we did not examine the variables to help select responders by OLVP in terms of diastolic function, this information and the relation between responders and outcome should be further examined.

Study limitations

First, The number of patients is too small to draw the definite conclusions. Further studies are clearly needed. Second, there was no control group for patients without use of patches, who were treated with SVR, therefore, it is difficult to directly compare the LV diastolic dysfunction in patients treated with and without use of patches. Third, the population was mixed including ischemic and non-ischemic heart failure because patients with non-ischemic heart failure are prevalent in Japan. Forth, we recognize that early changes in diastolic function and oxidative metabolism may not direct lead to an improved clinical outcome.

Conclusion

The present study demonstrated that a half of patients with severe dilated cardiomyopathy were responders for OLVP in terms of diastolic function. In these responders, oxidative metabolism significantly decreased, suggesting that OLVP reduced excessive metabolism during the diastolic phase, in part, via the improvement in diastolic function as well as the reduction in LV wall stress.

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Conflicts of interest None.

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LATE BREAKING CLINICAL TRIAL (JCS 2013)

Urgent Management of Rapid Heart Rate in Patients With Atrial Fibrillation/Flutter and Left Ventricular Dysfunction

– Comparison of the Ultra-Short-Acting β1-Selective Blocker Landiolol With Digoxin (J-Land Study) –

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Background: A rapid heart rate (HR) during atrial fibrillation (AF) and atrial flutter (AFL) in left ventricular (LV) dysfunction often impairs cardiac performance. The J-Land study was conducted to compare the efficacy and safety of landiolol, an ultra-short-acting β-blocker, with those of digoxin for swift control of tachycardia in AF/AFL in patients with LV dysfunction.

Methods and Results: The 200 patients with AF/AFL, HR ≥120 beats/min, and LV ejection fraction 25–50% were randomized to receive either landiolol (n=93) or digoxin (n=107). Successful HR control was defined as ≥20% reduction in HR together with HR <110 beats/min at 2 h after starting intravenous administration of landiolol or digoxin. The dose of landiolol was adjusted in the range of 1–10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ according to the patient's condition. The mean HR at baseline was 138.2±15.7 and 138.0±15.0 beats/min in the landiolol and digoxin groups, respectively. Successful HR control was achieved in 48.0% of patients treated with landiolol and in 13.9% of patients treated with digoxin (P<0.0001). Serious adverse events were reported in 2 and 3 patients in each group, respectively.

Conclusions: Landiolol was more effective for controlling rapid HR than digoxin in AF/AFL patients with LV dysfunction, and could be considered as a therapeutic option in this clinical setting. (*Circ J* 2013; **77:** 908–916)

Key Words: Atrial fibrillation; Atrial flutter; β-blocker; Landiolol; Left ventricular dysfunction

Atrial fibrillation (AF) and atrial flutter (AFL) are common arrhythmias in patients with left ventricular (LV) dysfunction. Over 20% of patients with heart failure exhibit AF.[1,2] In these patients, AF/AFL are often associated with a rapid ventricular response during the worsening of heart failure.[3,4] However, a sustained rapid ventricular response may

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The first seven authors contributed equally to this clinical trial (R.N., K.K., H.I., H.A., Y.S., T.Y., W.S.).

The members of the J-Land study group are listed in the Appendix.

Clinical Trial Registration: JapicCTI-111448 (http://www.clinicaltrials.jp/user/ctiMenu.jsp).

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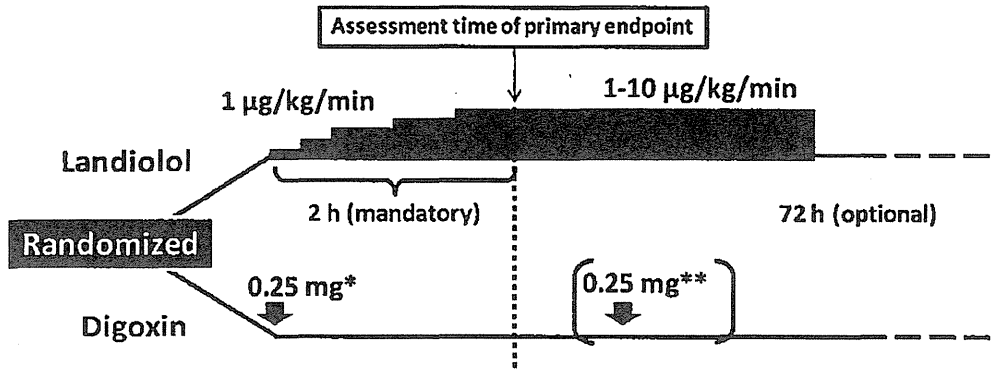

Figure 1. Study protocol. *Dose could reduce to 0.125 mg in patients being treated with oral digitalis preparations. **Additional doses of digoxin administered as deemed necessary.

further deteriorate cardiac function,[5] accelerating the symptoms of heart failure.[6–8]

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Intravenous administration of digoxin is considered the standard therapy for controlling the rapid ventricular response in AF/AFL patients with cardiac dysfunction or heart failure.[4,9] Although digoxin has some beneficial effects for treating heart failure, because of its positive inotropic effects, digoxin may also have a negative chronotropic effect as a result of vagal stimulation that develops much more slowly, often taking several hours to reach the maximal effect.[9,10] Short-acting parenteral β-blockers can act more rapidly than digoxin, and may provide swift control of the heart rate (HR) in these clinical settings. However, there is concern that β-blockers may depress cardiac function and further deteriorate ventricular dysfunction, accelerating heart failure.

Landiolol, an ultra-short-acting β-blocker, is rapidly metabolized to inactive forms in the blood and liver, resulting in a short half-life of approximately 4 min in human blood. In addition, it selectively binds to β1 receptors, with a β1 receptor selectivity (β1/β2) as high as 251.[11] Based on these properties, landiolol has been reported to be useful for treating several acute disorders, including arrhythmias during heart surgery,[12] acute myocardial infarction,[13] acute decompensated heart failure,[14] and refractory electrical storm.[15]

Ultra-short-acting β-blockers may be useful to control the HR with minimal effects on cardiac function because the negative inotropic effect is not sustained after decreasing the dose or stopping administration of these drugs. Therefore, the present study was designed to evaluate the efficacy and safety of intravenous landiolol for achieving rapid control of tachycardia in patients with AF/AFL and LV dysfunction.

Methods

Study Design and Patients

This study was designed as a central registration, prospective, multicenter, single-blind, randomized, parallel-group study for examining tachycardia in patients with AF/AFL and LV dysfunction. It was conducted in 95 hospitals in Japan between March 2011 and August 2012. The main inclusion criteria were: male or female inpatients aged ≥20 years; New York Heart Association (NYHA) class III or IV; and AF/AFL with an LV ejection fraction (EF) of 25–50% and a HR ≥120 beats/min. The main exclusion criteria were: necessity for electrical cardioversion; serious valve stenosis; confirmed or suspected hyperthyroidism; implantable cardiac pacemaker and/or implantable defibrillator; necessity for mechanical ventilation; and cardiogenic shock (systolic blood pressure (BP) <90 mmHg). The use of antiarrhythmic drugs, sympathomimetic drugs, sympatholytic drugs, defibrillator use, catheter ablation, and pacemaker therapy were prohibited from administration until completing all observations at 2 h after starting treatment. However, patients being treated with oral β-blockers (carvedilol or bisoprolol) or oral digitalis preparations for chronic heart failure, chronic AF, and/or chronic AFL could participate in the study under continued treatment without changes in their doses.

The enrolled patients gave informed consent before randomization to either treatment. The study protocol was approved by the institutional review boards at all of the participating institutions, and the study was conducted in accordance with the Declaration of Helsinki.

Study Protocol

The study protocol is shown in **Figure 1**. After enrolment, each patient was randomized to receive landiolol or digoxin using the permuted block method. In the landiolol group, continuous intravenous administration of landiolol was started at a dose of 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and titrated to a maximum dose of 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ according to the patient's condition. Landiolol was administered for ≥2 h and up to 72 h. In the digoxin group, digoxin was intravenously administered at an initial dose of 0.25 mg and could be uptitrated within 72 h according to the patient's condition. For patients treated with oral digitalis, the parenteral digoxin dose could be reduced to 0.125 mg according to the patient's condition to prevent digitalis intoxication.

The primary efficacy endpoint was the percentage of patients with both a HR <110 beats/min and ≥20% decrease from baseline at 2 h after administration. The secondary endpoints were HR at 0.5, 1, and 2 h, conversion to normal sinus rhythm, and subjective symptoms and objective findings (palpitations,

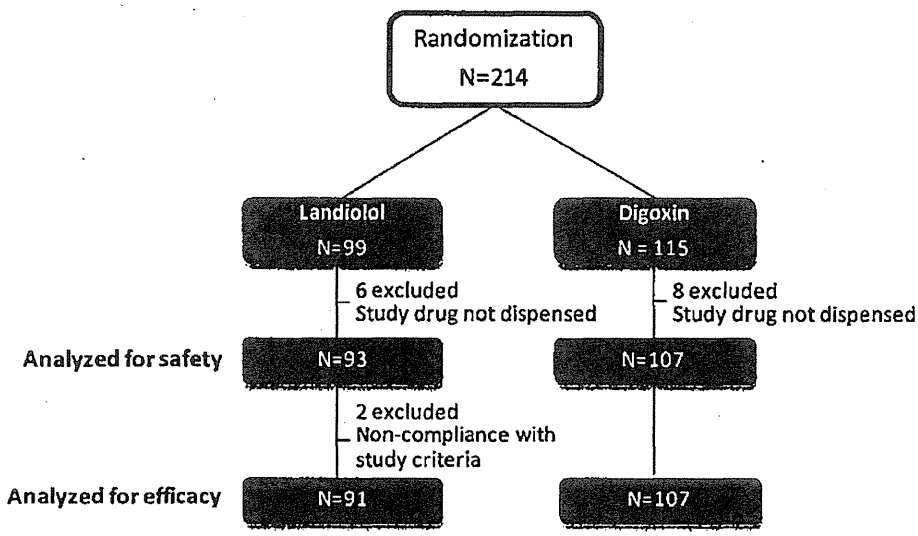

Figure 2. Patient disposition.

chest pain, dizziness, dyspnea, and edema) at these times.

The safety endpoint was the incidence of adverse events related or unrelated to the study drugs. Adverse events that resulted in death, were life-threatening, required hospitalization or prolonged hospitalization, resulted in persistent or significant disability/incapacity, and crucial medical events were classified as serious adverse events.

After completing the observations at 2 h after starting the administration of landiolol, it was replaced with an oral β-blocker, as deemed necessary, at the investigator's discretion.

Statistical Analysis

Data are expressed as the mean±standard deviation or percentages of patients. Student's t-test and χ^2 test were used to compare the means and percentages, respectively, between the 2 groups. The primary endpoint was compared between the 2 groups using a linear probability model with HR and LVEF measured immediately before starting the study drug as covariates. The changes in HR and BP after starting the study drugs were compared between the 2 groups using a linear mixed-effects model with adjustment for HR/BP and LVEF before starting the study drug. The following covariance structures were considered: unstructured, compound symmetrical, first-order autoregressive, and Toeplitz. The covariance structure that provided the best fit according to the Akaike information criterion was used in the analysis. Assessment times were treated as categorical factors. Student's t-test was used to compare outcomes between the 2 groups at each time, while the paired t-test was used to compare values between baseline and each time within each group. Bonferroni correction was used for multiple comparisons, except for the change in BP, which was assessed as a safety parameter. Subjective symptoms and objective findings (palpitations, chest pain, dizziness, dyspnea, and edema) were analyzed using the Wilcoxon rank sum test for comparisons between the 2 groups and the Wilcoxon signed rank sum test for comparisons within each group. Values of $P<0.05$ were considered statistically significant (2-sided). All analyses were performed using SAS version 9.2 for Windows (SAS Institute, Cary, NC, USA).

Results

Patient Disposition and Baseline Characteristics

The disposition of patients in this study is shown in **Figure 2**. A total of 214 patients were randomized to either landiolol (n=99) or digoxin (n=115). Of these, 14 patients were not treated (landiolol group, n=6; digoxin group, n=8) and 2 patients in the landiolol group did not comply with the protocol. Therefore, 200 patients (landiolol, n=93; digoxin, n=107) were included in the safety analysis set and 198 patients were included in the efficacy analysis set (landiolol group, n=91; digoxin group, n=107).

The demographics of the study patients are shown in **Table 1**. There were no differences in the general characteristics of the 2 groups. The mean age was 71.6±11.5 years, and 106 patients (53.0%) were male. The type of atrial tachyarrhythmia at entry was AF in 174 patients (87.0%), AFL in 21 patients (10.5%), and a mixture of AF/AFL in 4 patients (2.0%). The cardiovascular disease was hypertension in 133 patients (66.5%), ischemic heart disease in 30 patients (15.0%), and cardiomyopathy in 13 patients (6.5%). The mean HR was 138.1±15.3 beats/min and the mean LVEF was 36.6±7.6%. The NYHA class was III in 163 patients (81.9%) and IV in 36 patients (18.1%). Before starting study treatment, diuretics were used in 100 patients (50.0%), oral β-blockers were used in 41 patients (20.5%), and nitrate was used in 29 patients (14.5%).

Effects of Landiolol on AF and AFL

The changes in HR and BP for 2 h after starting the administration of landiolol and digoxin are shown in **Figure 3**. Landiolol and digoxin significantly decreased the HR from baseline for over 30 min after administration. However, the

Table 1. Baseline Characteristics of Patients With Atrial Fibrillation or Flutter and Left Ventricular Dysfunction

	Total (n=200)	Landiolol (n=93)	Digoxin (n=107)	P value
Demographic characteristics				
Age (years)	71.6±11.5	70.5±12.0	72.5±11.0	0.221
Male, n (%)	106 (53.0)	50 (53.8)	56 (52.3)	0.840
Weight (kg)	60.5±13.2	60.8±13.4	60.2±13.1	0.732
Baseline arrhythmia, n (%)				
Atrial fibrillation	174 (87.0)	80 (86.0)	94 (87.9)	0.095
Atrial flutter	21 (10.5)	8 (8.6)	13 (12.1)	
Atrial fibrillation or flutter	4 (2.0)	4 (4.3)	0 (0)	
Other	1 (0.5)	1 (1.1)	0 (0)	
History of heart failure, n (%)	120 (60.0)	57 (61.3)	63 (58.9)	0.728
Baseline CV disease, n (%)				
Hypertension	133 (66.5)	63 (67.7)	70 (65.4)	0.729
Ischemic heart disease	30 (15.0)	12 (12.9)	18 (16.8)	0.439
DCM	11 (5.5)	6 (6.5)	5 (4.7)	0.582
HCM	2 (1.0)	2 (2.2)	0 (0)	0.127
Hemodynamic parameters				
HR (beats/min)	138.1±15.3	138.2±15.7	138.0±15.0	0.934
SBP (mmHg)	125.7±21.8	124.6±19.8	126.6±23.5	0.523
DBP (mmHg)	84.2±19.2	81.5±16.5	86.5±21.1	0.068
LVEF (%)	36.6±7.6	36.4±7.9	36.7±7.3	0.753
Creatinine (mg/dl)	0.98±0.32	0.98±0.33	0.97±0.32	0.883
BNP (pg/ml)	661.7±561.0	688.0±663.8	639.0±456.6	0.540
NYHA class, n (%)				
III	163 (81.9)	71 (77.2)	92 (86.0)	0.108
IV	36 (18.1)	21 (22.8)	15 (14.0)	
Treatment before administration, n (%)				
Diuretic	100 (50.0)	48 (51.6)	52 (48.6)	0.671
hANP	67 (33.5)	28 (30.1)	39 (36.4)	0.343
β-blocker (oral)	41 (20.5)	18 (19.4)	23 (21.5)	0.708
ARB	31 (15.5)	13 (14.0)	18 (16.8)	0.579
Nitrate	29 (14.5)	11 (11.8)	18 (16.8)	0.317
Aldosterone antagonist	25 (12.5)	11 (11.8)	14 (13.1)	0.789
ACE inhibitor	17 (8.5)	7 (7.5)	10 (9.3)	0.645
Digitalis (oral)	8 (4.0)	6 (6.5)	2 (1.9)	0.099

Data are mean±standard deviation, or n (%).
One patient with PSVT who violated the study protocol was enrolled, but the NYHA class was missing.
ACE, angiotensin-converting enzyme; ARB, angiotensin type 1 receptor blocker; BNP, B-type natriuretic peptide; CV, cardiovascular; DBP, diastolic blood pressure; DCM, dilated cardiomyopathy; hANP, human atrial natriuretic peptide; HCM, hypertrophic cardiomyopathy; HR, heart rate; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PSVT, paroxysmal supraventricular tachycardia; SBP, systolic blood pressure.

HR was significantly lower in the landiolol group than in the digoxin group at 1 h (117.3 vs. 125.4 beats/min) and 2 h (110.2 vs. 122.3 beats/min) after starting administration. The magnitude of the reduction in HR was significantly greater in the landiolol group than in the digoxin group (mixed-effects model: group, P=0.0001; time, P<0.0001; interaction [group×time], P<0.0001). The change in HR from baseline to 2 h was −27.0± 13.3 beats/min in the landiolol group and −16.0±13.0 beats/min in the digoxin group. By contrast, the changes in systolic and diastolic BPs over time were not significantly different between the 2 groups (mixed-effects model: group, P<0.0001 and P=0.06; time, P=0.001 and P=0.03; interaction [group×time], P=0.14 and P=0.14, respectively). However, systolic BP was significantly different between the 2 groups at 30 min onward (30 min: 118.1 vs. 129.5 mmHg; 1 h: 112.9 vs. 127.9 mmHg; 2 h: 114.1 vs. 127.7 mmHg). Diastolic BP was also significantly different between the landiolol and digoxin groups at 30 min (79.7 vs. 85.3 mmHg) and 1 h (76.4 vs. 84.5 mmHg).

The results for the primary endpoint are shown in Figure 4. The percentage of patients with both a HR <110 beats/min and ≥20% decrease from baseline to 2 h after administration was determined to examine the influence of HR and LVEF at baseline. Overall, 48.0% (n=40/82) of patients in the landiolol group and 13.9% (n=13/98) of patients in the digoxin group achieved the primary endpoint, with a between-group difference of 34.1% (95% confidence interval, 22.1–46.2; P<0.0001). AF/AFL was converted to sinus rhythm within 2 h in 2 patients (2.2%) in the landiolol group and in 2 patients (1.9%) in the digoxin group. The mean dose of landiolol at 2 h was 6.7±3.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$. The percentage of patients who achieved the primary endpoint

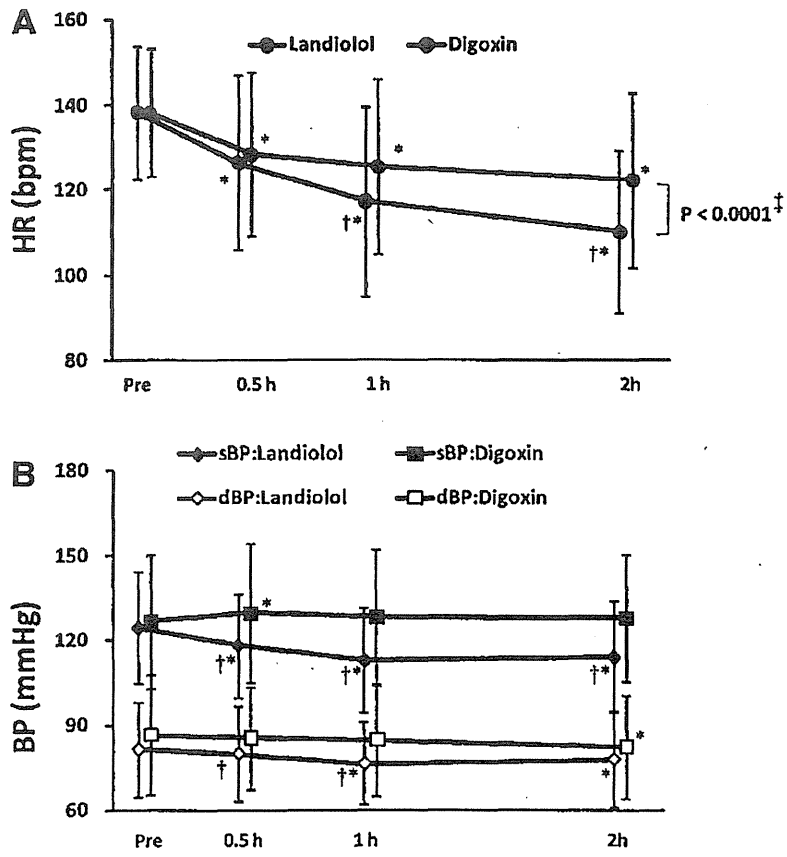

Figure 3. Time course of hemodynamic parameters of patients with atrial fibrillation/atrial flutter and left ventricular dysfunction treated with landiolol or digoxin. (**A**) Changes in mean heart rate (HR) during the study in the efficacy population (landiolol, n=87; digoxin, n=102). (**B**) Changes in blood pressure (BP) in the safety population (landiolol, n=93; digoxin, n=107). Data are mean±standard deviation. ‡Mixed-effects model used to compare data between the landiolol and digoxin groups (interaction: group×time). †P<0.05 vs. digoxin, *P<0.05 vs. baseline.

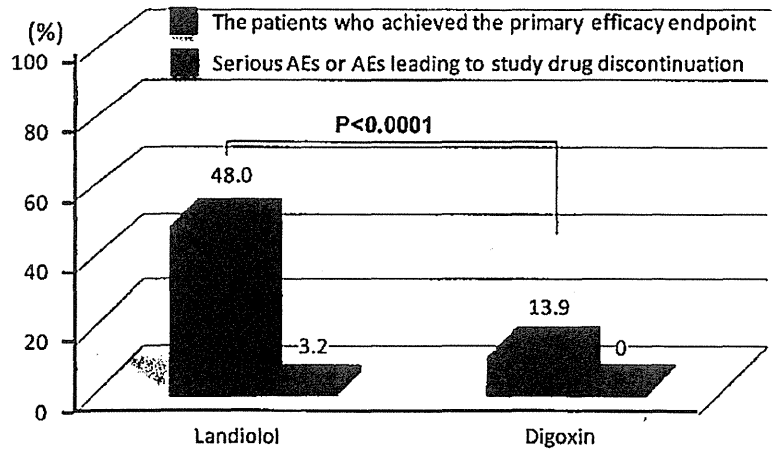

Figure 4. Comparison of the primary endpoint with the incidence of serious adverse events (AEs) or AEs resulting in study drug discontinuation. The percentages of patients with the primary endpoint (based on both heart rate <110 beats/min and ≥20% decrease in heart rate from baseline at 2 h after administration) were compared using a linear probability model with heart rate and left ventricular ejection fraction at baseline as covariates (landiolol, n=82; digoxin, n=98). Safety data are expressed as the incidence of serious AEs or AEs leading to study drug discontinuation within 2 h after administration (landiolol, n=93; digoxin, n=107).

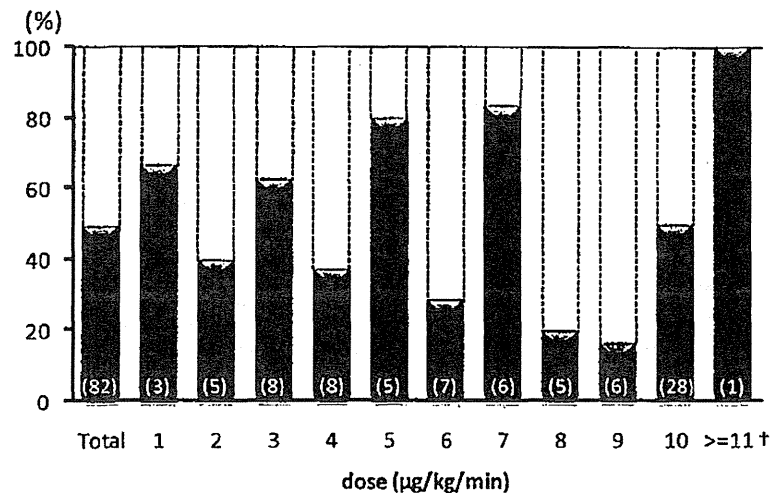

Figure 5. Percentages of patients who achieved the primary endpoint (based on both heart rate <110 beats/min and ≥20% decrease in heart rate from baseline at 2 h after administration) according to the dose of landiolol (total n=82). †One patient treated at a dose of 15 $\mu g \cdot kg^{-1} \cdot min^{-1}$ violated the protocol. Data are shown as the percentage of patients in each dose. Values in parentheses are the numbers of patients given each dose.

Table 2. Incidence of AEs in Patients With Atrial Fibrillation or Flutter and Left Ventricular Dysfunction Treated With Landiolol or Digoxin

	Landiolol (n=93)		Digoxin (n=107)	
	0–2 h	Total	0–2 h	Total
All, n (%)	8 (8.6)	30 (32.2)	2 (1.9)	35 (32.7)
Any serious AE, n (%)	1 (1.1)	2 (2.2)	0 (0)	3 (2.8)
Any AE leading to study drug discontinuation, n (%)	3 (3.2)	3 (3.2)	0 (0)	0 (0)
AEs occurring in >3%, n (%)				
Hypotension	3 (3.2)	7 (7.5)	0 (0)	4 (3.7)
Vomiting	0 (0)	4 (4.3)	0 (0)	1 (0.9)
Nausea	0 (0)	3 (3.2)	0 (0)	0 (0)
Increased creatinine*	0 (0)	3 (3.2)	0 (0)	3 (2.8)
Increased urea*	0 (0)	3 (3.2)	0 (0)	1 (0.9)
Constipation	0 (0)	0 (0)	0 (0)	4 (3.7)

Data are n (%). "0–2 h" included the number of patients with events occurring within 2 h after starting treatment. "Total" included the number of patients with events occurring between the start of treatment and the final observation. Only AEs occurring at a frequency of ≥3% are shown.
*Defined as an increase in values from normal to abnormal or worsening of the parameter from baseline; these events were judged by the investigators as an AE based on the clinical significance of the change. AEs, adverse events.

Table 3. Changes in Parameters at the Final Observation in Patients With Atrial Fibrillation or Flutter and Left Ventricular Dysfunction Treated With Landiolol or Digoxin

	Landiolol (n=93)		Digoxin (n=107)	
	Pre	Final	Pre	Final
HR (beats/min)	138.2±15.7	98.3±17.6	138.0±15.0	102.3±19.8
SBP (mmHg)	124.6±19.8	113.3±18.4	126.6±23.5	115.5±18.0
DBP (mmHg)	81.5±16.5	72.8±14.3	86.5±21.1	72.1±15.1
LVEF (%)	36.4±7.9	43.1±13.1	36.7±7.3	44.2±11.0
Creatinine (mg/dl)	0.98±0.33	0.99±0.35	0.97±0.32	0.94±0.31
NYHA class, n (%)				
None		0 (0)		1 (0.9)
I		12 (13.6)		12 (11.3)
II		50 (56.8)		51 (48.1)
III	71 (77.2)	24 (27.3)	92 (86.0)	40 (37.7)
IV	21 (22.8)	2 (2.3)	15 (14.0)	2 (1.9)

The final observation was performed at 48 h after the end of administration of landiolol or at 48 h after the final dose in the digoxin group. Abbreviations as in Table 1.

in the landiolol group at each dose is shown in **Figure 5**. The effective dose of landiolol ranged from 1 to 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ without dose-dependency.

The changes in subjective symptoms and objective findings (palpitations, chest pain, dizziness, dyspnea, and edema) during the study treatment are shown in **Table S1**. Palpitations, dyspnea, and edema improved significantly from baseline to 2 h in both groups. However, there were no clinically relevant differences in subjective symptoms or objective findings between the 2 groups. The mean duration of treatment with landiolol was 20.4±20.8 h (range, 0.8–72 h), and the mean dose of landiolol throughout the treatment was 6.3±3.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$. After the study treatment period, landiolol was replaced bisoprolol in 47 patients (50.5%) and by carvedilol in 27 patients (29.0%), at maintenance doses of 1.8±1.3 mg and 3.2±2.7 mg, respectively.

Safety

The incidence of adverse events is shown in **Table 2**. Adverse events occurred in 30 patients (32.3%) in the landiolol group and in 35 patients (32.7%) in the digoxin group, which was not statistically significant (P=0.95). During the 2-h treatment period, adverse events occurred in 8 patients (8.6%) in the landiolol group and in 2 patients (1.9%) in the digoxin group, which was statistically significant (P=0.029). Hypotension was reported as an adverse event in 7 patients (7.5%) in the landiolol group and in 4 patients (3.7%) in the digoxin group, showing no significant difference between the 2 groups (P=0.24). Vomiting and nausea were reported in 4 patients (4.3%) and 3 patients (3.2%), respectively, in the landiolol group. Vomiting was reported in 1 patient (0.9%) in the digoxin group, but nausea was not reported in this group.

Serious adverse events were reported in 2 patients in the landiolol group (congestive heart failure and embolic stroke in 1 patient each) and in 3 patients in the digoxin group (sinus arrest, diabetes insipidus, and pneumonia in 1 patient each). One patient in the landiolol group developed acute exacerbation of congestive heart failure at 12 h after the end of administration of landiolol. Despite the intensive treatments, the patient died at 31 h after the end of administration of landiolol. The administration of landiolol was stopped in 3 patients because of an adverse event (embolic stroke, hypotension, and asthma in 1 patient each).

The changes in the hemodynamic parameters, renal function, and symptoms at the final observation are shown in **Table 3**. The period to the final observation was 66.6±22.5 h in the landiolol group and 49.9±11.9 h in the digoxin group. None of the laboratory parameters worsened from baseline to the end of the study in either group. The brain natriuretic peptide levels did not increase from baseline in either group (**Figure S1**).

Discussion

The results of this study show that continuous intravenous administration of landiolol in a dose-escalating manner effectively controlled rapid HR in patients with AF/AFL and LV dysfunction. Landiolol and digoxin were effective in 48.0% and 13.9% of patients, respectively, at 2 h after starting treatment, indicating that the ultra-short-acting landiolol is more useful than the slow-acting digoxin. Regarding the safety of these drugs for rapid control of HR, the incidence of hypotension was similar in both groups. During treatment with landiolol, which rapidly reaches steady state and has a half-life of 4 min, the risk of hypotension may be low because its dose can be carefully adjusted according to the patient's condition. Other adverse effects associated with a reduction in HR include gastrointestinal symptoms such as nausea/vomiting caused by blood flow stasis. However, there were no abnormal changes in laboratory data, including serum bilirubin levels.

It has been reported that the control of HR in patients with tachycardic AF/AFL helps to prevent worsening of heart failure and ventricular dysfunction, because it contributes to improvements in circulatory dynamics and subjective symptoms.[16–18] However, the optimal target HR in the treatment of AF/AFL in patients with LV dysfunction has not been clearly established. In patients with LV dysfunction, a rapid and vigorous decrease in HR might be detrimental if accompanied by a decrease in cardiac output. However, in the RACE II study, which was conducted in patients with persistent AF and normal to moderate LV dysfunction, there were no differences in prognosis, including mortality, incidence of heart failure, and improvements in subjective symptoms, between the lenient control (resting HR <110 beats/min) and strict control (resting HR <80 beats/min and HR during moderate exercise <110 beats/min) groups.[19] In the present study conducted in patients with LV dysfunction and NYHA class III or IV symptoms, the target HR of <110 beats/min, corresponding to the lenient criterion in the RACE II study, may be reasonable based on the results of earlier studies. In addition, a 20% decrease in HR from baseline has been conventionally used to verify the drug-induced HR reduction in AF.[20,21] Accordingly, the primary endpoint in this study combined both criteria.

In general, the optimal dose of β-blockers in patients with LV dysfunction should be determined according to the patient's cardiac function and general condition. It should also be noted that the response to β-blockers in patients with AF varies depending on polymorphisms (eg, G389R and S49G) in the $\beta 1$ receptor gene.[22] In fact, the present study showed that the optimal dose varied among the patients with variable response to landiolol. Therefore, the optimal dose of β-blocker for HR control cannot be determined before treatment. The dosage of rate-controlling drugs for treating AF/AFL in patients with LV dysfunction should be highly adjustable, according to the patient's hemodynamic response. The efficacy and safety results of this study provide support for the ultra-fast-acting and easily adjustable landiolol for swift control of rapid HR in patients with AF/AFL and LV dysfunction. However, in the present study, there were no significant differences between the 2 groups in the subjective symptoms reported within 2 h after starting administration. The rapid decrease in HR elicited by landiolol may not necessarily be associated with symptomatic relief in these patients. These findings suggest that it is difficult to evaluate how rapid HR contributes to the hemodynamic status and symptoms of heart failure in patients with AF/AFL.

The guidelines of the American Heart Association and the European Society of Cardiology recommend digitalis and amiodarone for acute rate-control therapy in patients with AF and LV dysfunction.[9,23,24] Although amiodarone is classified as a rhythm-control drug, it can also decrease the HR because it blocks K^+ channels, Ca^{2+} channels, and β receptors. However, because amiodarone has a long half-life, it is difficult to adjust its dose according to the patient's condition.

In the present study, we observed better control of HR with landiolol than with digoxin. As landiolol was the only intravenous β-blocker used in this study, the efficacy of esmolol, propranolol, and amiodarone in this setting remains unknown. Thus, we cannot confirm whether landiolol is more effective than these drugs. Nevertheless, landiolol may be easier to use