Table 3: Factors related to PGD

Factors	*n*	*P*-value
Donor-related factors		
High dose inotropic support	11	0.0089
Recent cardiac arrest	11	0.8
Female to male	11	0.9
LVEF < 55%	6	0.0383
Elderly (>50 years old)	6	0.85
LVDd < 36 mm	5	0.0002
R/D mismatch (body weight ratio < 0.8)	2	-
LV hypertrophy	2	-
Intracranial haemorrhage	22	0.27
Recipient related factors		
History of stroke	17	0.15
Exit site infection of LVAD	7	0.0812
Creatinine clearance < 30 ml	4	0.77
PVR > 4.0 wood unit	0	-

High dose inotropic support indicates patients who required intravenous infusions of more than 10 μg/kg/min of inotropic agents or epinephrine. Recent cardiac arrest indicates patients who required resuscitation. History of stroke indicates patients who suffered from stroke or haemorrhagic stroke during LVAD support. Exit site infection indicates patients who required intra-venous infusion of antibiotics due to LVAD exit site infection.
LVEF: left ventricular ejection fraction; LVDd: left ventricular diastolic diameter; R/D mismatch: mismatch of body weight ratio of recipient/donor; LV hypertrophy: left ventricular hypertrophy (echocardiographic diagnosis of left ventricular septum thickness >13 mm and left posterior wall thickness >13 mm); PVR: pulmonary vascular resistance.

Table 4: Post-transplant cardiac function, comparison between patients with and without PGD

Variables	With PGD (*n* = 7)	Without PGD (*n* = 29)	*P*-value
Cardiac index, day 0 (l/min/m^2)	1.8 ± 0.4	3.1 ± 0.5	<0.0001
Cardiac index, day 1 (l/min/m^2)	2.3 ± 0.5	3.2 ± 0.6	0.0027
Cardiac index, day 2 (l/min/m^2)	2.3 ± 0.5	3.3 ± 0.9	0.024
Mean pulmonary pressure, day 0 (mmHg)	18 ± 3	20 ± 4	0.24
Mean pulmonary pressure, day 1 (mmHg)	17 ± 3	18 ± 4	0.65
Mean pulmonary pressure, day 2 (mmHg)	18 ± 5	18 ± 3	0.93
LV Dd, 1 week (mm)	37 ± 6	41 ± 4	0.19
LV Ds, 1 week (mm)	22 ± 7	25 ± 4	0.0932
LVEF, 1 week (%)	71 ± 14	76 ± 21	0.36
LV Dd, 1 month (mm)	38 ± 3	41 ± 4	0.12
LV Ds, 1 month (mm)	22 ± 4	25 ± 4	0.0992
LVEF, 1 month (%)	74 ± 6	70 ± 7	0.11
Postoperative maximum CKMB (U/l)	63 ± 37	75 ± 54	0.51
PIMI score (grades 0–3)	1.7 ± 0.8	1.1 ± 0.9	0.15
Days in intensive care unit	6.4 ± 3.7	6.6 ± 4.2	0.97

LV: left ventricular; Dd: diastolic diameter; Ds: systolic diameter; LVEF: left ventricular ejection fraction; CKMB: creatine kinase-MB; PIMI score: postoperative ischaemic myocardial injury score.

inotropic requirement in the donor ($P = 0.0008$), LVEF less than 55% ($P = 0.0383$) and small LV diastolic diameter less than 36 mm ($P = 0.0002$) (Table 3). On the other hand, an episode of recent cardiac arrest ($P = 0.8014$), transplantation from female to male ($P = 0.8990$), transplantation from a donor older than 50 years old ($P = 0.8506$), recipient/donor body weight ratio less than 0.8 (0.2612) and left ventricular hypertrophy did not affect postoperative graft dysfunction. Prolonged ischaemic time longer than 4 h occurred in only one case (4 h 15 min) and PGD did not develop. The cause of brain death did not affect the outcome in our patient group. Furthermore, recipient-related factors such as history of stroke, including haemorrhagic stroke, and LVAD exit site infection that required intravenous antibiotics were analysed as well, although there were no recipient-related factors associated with PGD.

The outcome of patients with PGD was also assessed. There were no significant differences between patients with and without PGD in regard to postoperative maximum creatine kinase-MB, postoperative mean pulmonary artery pressure, echocardiographic data at 1 week and 1 month including LVEF, and PIMI score at the first biopsy, although the cardiac index was lower in patients with PGD (Table 4).

Preservation solution

We also assessed the effects of the preservation solution used for the donor heart after harvesting. The first 6 donor hearts were preserved with St Thomas solution, while Celsior was used in the next 30 cases. There were no significant differences in regard to postoperative cardiac function between the solutions, as indicated by cardiac index, mean pulmonary pressure and LVEF (Table 5). However, the PIMI score was significantly lower in patients with hearts preserved using Celsior, which corresponded with our findings that the level of postoperative maximum CKMB was also significantly lower in those patients.

Table 5: Post-transplant cardiac function and ischaemic damage, comparison between preservation with Celsior and St Thomas solutions

Variables	Celsior (*n* = 30)	St Thomas (*n* = 6)	*P*-value
Cardiac index, day 0 (l/min/m^2)	2.8 ± 0.7	3.3 ± 0.7	0.0936
Mean pulmonary pressure, day 0 (mmHg)	19 ± 4	18 ± 1	0.25
LVEF, 1 week (%)	69 ± 9	65 ± 16	0.72
LVEF, 1 month (%)	71 ± 6	68 ± 9	0.47
Postoperative maximum CKMB (U/l)	58 ± 35	145 ± 58	0.0013
PIMI score (grade 0–3)	1.0 ± 0.8	2.3 ± 0.8	0.0054

LVEF: left ventricular ejection fraction; CKMB: creatine kinase-MB; PIMI score: postoperative ischaemic myocardial injury score.

Current clinical status

All patients were discharged from the hospital with good cardiac function. At the most recent follow-up examination, all except the

one death case, were NYHA class I or II. Furthermore, no recipient had pathological chronic rejection greater than grade 3.

DISCUSSION

The discrepancy between organ supply and demand in the field of heart transplantation has led to an increase in numbers of patients on waiting lists. Recent developments in LVADs and improvements in patient management have been very beneficial for patients with a failing heart, and allow bridging to transplantation. In the present series, the average LVAD support period was 2.5 years. However, patients with an LVAD have elevated risks of stroke, haemorrhagic stroke and infection, which are life-threatening complications.

Great efforts have been made to provide alternatives to heart transplantation, such as LVAD destination therapy with less complicated devices or cell transplantation for functional recovery of the damaged heart. Nevertheless, heart transplantation remains the gold standard for a failing heart [16, 17]. Although the regulations have been changed in Japan, resulting in a greater than 5-fold increase in number of donors, the waiting period remains the same, because demand has also increased. As a result, greater acceptance of marginal donors is essential.

In the present study, 28 (78%) donors were considered to be marginal as defined by criteria that included old age, high inotropic support, recent cardiac arrest, left ventricular hypertrophy, reduced left ventricular contraction, prolonged ischaemic time and donor-recipient size mismatch. However, only seven (19%) recipients showed postoperative LOS, of whom five did not require mechanical support. Fortunately, we had no hospital mortality and a 95% survival rate after 10 years. These results may be attributed to not only appropriate preservation methods and post-transplant management, but also donor selection. Since there were fewer chances for heart transplantation when compared with other countries, more attention had been paid to donor-recipient matching, such as donor-recipient weight ratio, dosage of catecholamine and ischaemic time. Moreover, maximum efforts were conferred to decrease these risks, such as replacing catecholamine by vasopressin to maintain systolic blood pressure, or preserving donor hearts with Celsior solution and transferring them mainly by in combination of helicopter and air planes. When the donor heart matched one of these criteria, careful attention was given to not overlap any two of those elements. There were 10 donors (28%) who were considered marginal by two matching criteria, while there was none considered to be marginal by more than three matching criteria. Furthermore, more attention was paid when donor-recipient size mismatch and LV hypertrophy were observed [18–20], which resulted in a limited number of donors who showed donor-recipient size mismatch or LV hypertrophy in our series (Table 3). In our analysis of donor condition, small ventricular size was shown to be a significant factor associated with postoperative LOS, as well as reduced LVEF and high inotropic requirement.

Donor-recipient size mismatch has been identified as a significant risk factor for PGD, as has female to male transplantation, which is likely associated with size mismatch [18, 20]. Small ventricular diastolic diameter is also expected to cause the same condition. Thus, it is important to consider LV size as well as donor-recipient size mismatch for donor selection. However, even with a small heart or a heart from a small donor, once the initial complicated period of LOS has passed, excellent long-term outcomes may be anticipated [21]. Therefore, acceptance of donors with a small left ventricular diameter might be reasonable when there are no other known disadvantages.

It is important to note that high-dose inotropic requirement for the donor heart implies not only impaired LV function, but also the possibility of continuous myocardial damage from increased oxygen demand and depletion of high energy phosphates from the myocardium [8]. Thus, a donor heart with reduced LV contraction that requires high dose inotropic support should be carefully evaluated by determining whether the myocardial damage is permanent. For optimal haemodynamic management to protect organ damage, arginine vasopressin is being used more often to maintain systolic pressure with lower levels of inotropic support, which may be helpful for appropriate evaluation [22].

All of our patients with postoperative LOS recovered cardiac function quickly, then were discharged from the intensive care unit about 6 days later and returned home without major concerns. Echocardiogram findings revealed nearly total recovery of LV contraction after 1 week. Optimal postoperative management, such as appropriate use of NO inhalation and inotropes, and proper indications for mechanical support should result in good outcomes. The present results suggest that cautious donor selection is essential when the donor heart has a small ventricular diameter or requires a high level of inotropic support. However, long-term survival in recipients with marginal donor hearts can be anticipated with adequate treatment.

A long preservation period is another hurdle to overcome for successful heart transplantation. To maximize the cardiac function of the donor heart postoperatively, a low level of ischaemic damage is critical. Preservation with Celsior may be less invasive and decrease ischaemic insult when compared with St Thomas solution. We found that creatine kinase-MB and postoperative PIMI scores were significantly lower in the Celsior group, although cardiac function was not different. Therefore, Celsior may contribute to expand acceptance for marginal donors, especially when a prolonged preservation period is expected.

Fortunately, we experienced only one VA-ECMO case and two IABP cases, but these mechanical supports were always on standby. Based on the excellent results by optimistic introduction of VA-ECMO for PGD, the hurdle for the use of them should be set low [3].

Although the number of patients analysed is small, our 10-year survival rate was 95%. Based on this excellent long-term result, we consider that acceptance of marginal donor hearts can be extended, when the donor is selected based on the donor-recipient matching and mechanical supports such as IABP and VA-ECMO are on standby. Furthermore, to maintain good long-term results in recipients in stable condition and also rescue marginal recipients, development of an alternate recipient list may provide a partial solution, although the concept of 'marginal donors for marginal recipients' is not commonly accepted at this time.

Conflict of interest: none declared.

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APPENDIX. CONFERENCE DISCUSSION

Dr A. Pavie *(Paris, France)*: Yours is an unusual series because you performed only three transplantations per year which is quite a different experience from other transplant teams. A lot of the patients were supported on cardiac assist, 30 out of 36 patients, which is quite rare. How many other patients did you have on assist during this same period?

Dr Fujita: As you know, the waiting period for heart transplantation is pretty long, about three years in Japan. We selected to implant LVAD in patients who were mostly candidates for heart transplantation. The survival rate at three years for the patients with LVAD was about 60% and surviving patients undergo heart transplantation.

Dr Pavie: You had only LVAD patients on cardiac assist. Were any of your patients on biventricular support?

Dr Fujita: Only LVAD at the time of cardiac transplant.

Dr Pavie: I would like also to comment on your definition of marginal donor. When we look at your criteria, for us in Europe they are clearly not considered marginal donors. The mean level of drugs is low. You said in your series that seven patients had primary graft dysfunction. We have some concern about that. You put a patient on ECMO, and you are able to wean this patient after one day. Generally such patients stay one, two, or three weeks on ECMO before recovering good myocardial function. You wait a long time for a donor, but you have an excellent donor when you carry out the transplantation. It is an excellent paper but with a very particular approach which is difficult to compare with the European experience.

Dr Fujita: I agree with you.

D F. Beyersdorf *(Freiburg, Germany)*: As Dr Pavie has already said, in Europe we have completely different results, unfortunately, worse results. And 10 years' survival of 95% is unknown to me. I know that in Japan you have a long history of resistance to transplantation, so that is the reason why you are not doing so many transplants. But could you give us some idea why the results are so extraordinarily good?

Dr Fujita: I think the major reason is we do not have many ischaemic cardiomyopathy patients. The idiopathic dilated cardiomyopathy patient is younger, and very few are in the vascular programme. This is the reason for the good long-term results I think. And the other thing is we have a special system called 'medical consultant system', in which the cardiac surgeon always goes to the donor site, and gives advice in order to better maintain the patient.

Dr Beyersdorf: So you think that the treatment of the donor is often suboptimal? For example, in the UK, I heard the system to treat donors is much better than in other countries in Europe. So you think this is one of the main reasons?

Dr Fujita: Yes.

Dr D. Esmore *(Victoria, Australia)*: The previous report by the Italian group suggested they only had 5.9% of their patients on VADs at the time of transplant. The world trend is towards your experience. Norman Shumway made a comment about six or seven years ago that he believed that everyone transplanted down the track will actually be transplanted off a VAD. So what you have is a group of VAD-supported patients who are stable at home, presumably, with a large investment in their wellbeing who will be potentially transplanted with donor organs that are perhaps older, perhaps of lesser quality, i.e. 'marginal'. And, therefore, the risks perhaps that you are referring to in regards to 30-day mortality are probably only going to increase over time. The data for VAD-supported patients suggests that they do as well post-transplant as a non-VAD patient, but we do know the VAD pathway is more complex.

So actually what you are experiencing is a low organ donation rate, a high VAD implant rate, and still getting good outcomes post-transplantation. I think this is something that is going to be a challenge down the track for all of us. The two-and-a-half or three-hour heart transplant that you complete and then go out to lunch, that is the past. Heart transplantation for the future will be in a mechanically-supported waiting list patient, often marginal donor cardiac allografts, with the challenge being to achieve the sort of results that you have presented. And I think that is where heart transplantation really is today. I comment on that and seek your response.

Dr Fujita: I think our experience is very small, so during the waiting period, the very long waiting period, we have automatically selected a good recipient. So the situation in the United States or Europe, where the patient gets worse and then they get their heart transplant in one month, is not realistic for us. Our patient stays in good condition for longer and gets a heart transplant. That is why we get a good result I guess.

Dr Esmore: But as for your mechanical support, I think the majority of patients only had a balloon pump, and two had ECMO and a balloon pump. So your primary graft failure, although present, was not actually associated with a requirement for VAD support, and the potential mortality associated with that and longer term support. With your donor rate being low, you may be pressured to use marginal donors, but they were not perhaps that 'marginal' in your study given the aforementioned discussion. As the session moderator said, you still achieved very good results, and I think this is where the future of heart transplantation will perhaps be going for all of us.

Association between length of stay, frequency of in-hospital death, and causes of death in Japanese patients with acute heart failure syndromes☆

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Neither studies nor guidelines have suggested criteria for determining the optimal length of stay (LOS) for patients hospitalized with acute heart failure syndromes (AHFS) [1,2]. The LOS of patients with AHFS is much longer in Japan (range of median; 18–21 days) than in Western countries (range of median; 4–10 days) because of differences in the health insurance system [3]. In fact, Japanese hospitals generally provide rehabilitation and nursing home care in addition to acute medical care for AHFS patients [3,4]. This suggests that the in-hospital outcome in Japan is likely to largely depend on the pathogenesis of heart failure (HF), its severity, and the quality of inpatient care rather than on factors related purely to the healthcare system. Accordingly, to investigate when and how AHFS patients actually die during hospitalization, we evaluated the association between the LOS, frequency of in-hospital death, and causes of in-hospital death in patients hospitalized for AHFS.

As a nationwide hospital-based prospective cohort study, the Acute Decompensated Heart Failure Syndromes (ATTEND) registry study accumulates data on AHFS patients admitted to 52 hospitals from all regions of Japan from April 2007 to December 2011. The design, methods, and patient profile of this study have been described previously [5]. In this study, the association of the LOS with in-hospital all-cause death, cardiac death (defined as HF death, sudden death, or other cardiac death), and non-cardiac death was evaluated for each 7-day period after admission. In addition, the incidence of HF death, sudden death, and other cardiac death during hospitalization was examined. This study is being conducted in accordance with the principles of the Declaration of Helsinki. Institutional review board approval was obtained at each participating medical center prior to commencing the study, and all patients provide written informed consent to enrollment. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology. This report of the study was descriptive. Data are presented as the mean ± SD, median with interquartile range, or frequency. An independent center (STATZ Institute inc, Tokyo, Japan) performed all analyses using SAS software (version 9.1, SAS Institute, Cary, NC, USA).

A total of 4841 patients with AHFS were enrolled. Their baseline clinical characteristics are displayed in Table 1. The median LOS in AHFS patients was 21 (14–32) days. The all-cause mortality rate during hospitalization was 6.4% (n = 311), with 218 cardiac deaths (70%) and 93

Table 1
Baseline characteristics of the patients with AHFS (n = 4841).

Characteristic	No. (%)
Age, yrs	73.0 ± 13.8[a]
Women	2036 (42.0)
Ischemic etiology	1510 (31.2)
Hypertensive etiology	857 (17.7)
Idiopathic dilated etiology	609 (12.6)
Valvular etiology	938 (19.4)
Left ventricular systolic dysfunction (EF<40%)	2581 (53.3)
Medical history	
Prior hospitalization for heart failure	1748(36.1)
Hypertension	3361 (69.1)
Dyslipidemia	1772 (36.6)
Diabetes mellitus	1636 (33.8)
Chronic obstructive pulmonary disease	589 (12.2)
Stroke/transient ischemic attack	675 (13.9)
Medications prior to admission	
Loop diuretic	2217 (45.8)
Spironolactone or Eplerenone	944 (19.5)
Thiazide diuretic	331 (6.8)
ACE inhibitor	700 (14.5)
Angiotensin receptor blocker	1674 (34.6)
Beta-blocker	1618 (33.4)
Calcium-channel blocker	1384 (28.6)
Digoxin	609 (12.6)
Nitrate	333 (6.9)
Aspirin	1578 (32.6)
Statin	1129 (23.3)
Intravenous medications during hospitalization	
Furosemide	3689 (76.2)
Any Vasodilator	3789 (78.3)
Any Inotrope	891 (18.4)
Systolic blood pressure, mm Hg	145.6 ± 36.6[a]
Diastolic blood pressure, mm Hg	82.6 ± 22.6[a]
Heart rate, beats/min.	98.6 ± 29.1[a]
Brain natriuretic peptide, pg/ml	706 [362–1285][b]
Blood urea nitrogen, mg/dl	27.8 ± 26.0[a]
Serum creatinine, mg/dl	1.44 ± 1.66[a]
Serum sodium, mEq/l	139.3 ± 4.6[a]
Hemoglobin, g/dl	12.0 ± 2.6[a]
C-reactive protein, mg/dl	0.57 [0.20–1.80][b]
Clinical features on admission	
Paroxysmal nocturnal dyspnea	2560 (52.9)
Orthopnea	3057 (63.1)
Rales	3442 (71.1)
Jugular venous pulsation	2555 (52.8)
Peripheral edema	3235 (66.8)
NYHA functional class	
III	1826 (37.7)
IV	2106 (43.5)

AHFS = acute heart failure syndromes; EF = ejection fraction; NYHA = New York Heart Association.
[a] Mean ± SD.
[b] Median [interquartile range].

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deaths from non-cardiac causes (30%). The number of all-cause deaths was evaluated for each 7-day period after admission. After peaking in the first 7 days, all-cause deaths declined during hospitalization, so there was an inverse correlation between the LOS and in-hospital death. Similarly, the number of cardiac deaths was highest during the first 7 days after admission and then declined over time (Fig. 1A). In contrast, the number of non-cardiac deaths increased up to 21 days after admission and then tended to decrease (Fig. 1A). We also examined the incidence of HF death, sudden death, and other cardiac deaths during hospitalization (Fig. 1B). Of the 218 in-hospital cardiac deaths, 184 were due to HF (84.4%), 21 were sudden deaths (9.6%), and 13 were other cardiac deaths (6.0%). The incidence of HF death was higher at all periods during hospitalization than that of sudden death or other cardiac death. Of the 44 cardiac deaths during the first 7 days after admission, 10 (22.7%) were sudden deaths. The frequency of sudden death was much higher during the first 14 days after admission than at any other time, with 71.4% of sudden deaths occurring during this period. On the other hand, other cardiac deaths were scattered throughout the entire period of hospitalization.

Our comparison of in-hospital cardiac and non-cardiac deaths showed differences in mortality trends. Recently, it was suggested that a disease-specific endpoint, such as cardiovascular death, might be a superior choice for studies of AHFS compared with all-cause mortality [6]. The mechanisms underlying the differences between cardiac and non-cardiac death during hospitalization are unclear, but some assumptions can be made. In AHFS patients, the cardiac death rate might be relatively high as the severity of HF increases and could often be high in the early period after admission. In contrast, previous studies have illustrated the importance of concurrent stroke, renal disease, and lung disease in prolonging the LOS for HF patients, suggesting that non-cardiac death might be observed in the late phase of hospitalization [7].

Our study also indicated the importance of sudden death in AHFS patients during hospitalization. In patients with chronic or advanced HF, it has been reported that approximately half of all-cause deaths are sudden and unexpected [8]. However, there is little information about the frequency of sudden death in AHFS patients. Our data showed that sudden death was responsible for approximately 10% of all cardiac deaths during hospitalization and for approximately one-fourth of cardiac deaths during the first 7 days, suggesting that the risk of sudden death might increase with the severity of HF [8]. Therefore, it seems that an aggressive therapeutic strategy targeting not only HF death, but also sudden death, should be considered for AHFS patients during the early phase after admission.

There are some limitations to consider when interpreting the results of our study. In particular, the LOS is affected by many factors [9], but we did not examine the association among the LOS, demographic variables at admission, and treatments during hospitalization because this study was focused on the association among the LOS, frequency of in-hospital death, and causes of death. Therefore, further investigation will be needed to clarify determinants of the LOS for AHFS patients.

In conclusion, our findings suggest that better understanding of the association among the LOS, frequency of in-hospital death, and causes of death could improve the estimation of the short-term prognosis for AHFS patients and might support targeted management of specific AHFS populations. However, further investigations will be necessary to clarify the association between the LOS, in-hospital death, and causes of death in AHFS patients.

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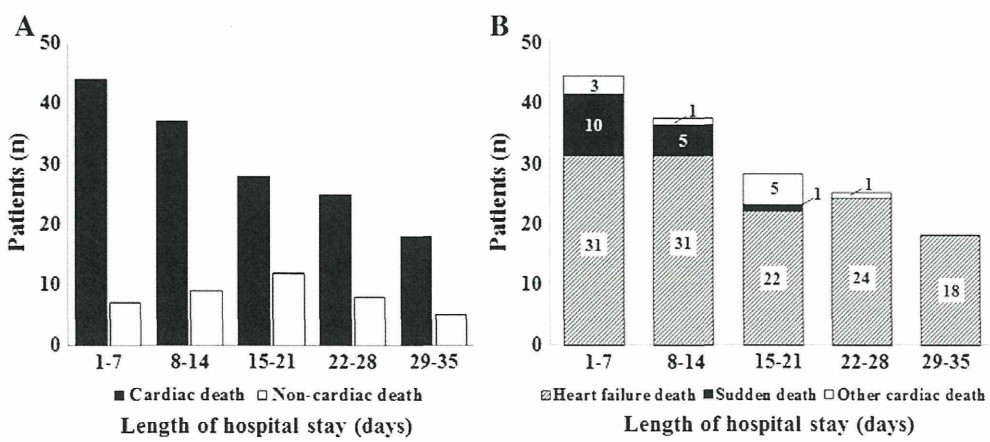

Fig. 1. In-hospital cardiac and non-cardiac deaths stratified according to the length of stay. (A) Number of cardiac deaths and non-cardiac deaths during hospitalization. (B) Number of heart failure deaths, sudden deaths, and other cardiac deaths during hospitalization.

Hospital: Koichi Nakao, Tadashi Sawamura, Toshiaki Nuki, Michiru Shoji, Naoko Takahashi; Shonan Dai-ichi Hospital: Koichi Shimamura, Michitaka Nagashima, Katsuya Kajimoto; Tokyo Medical University Hospital: Yoshifumi Takata, Manabu Miyagi, Nobuhiro Tanaka, Akira Yamashina; Saiseikai Futsukaichi Hospital: Shin-ichi Ando, Toshiaki Kadokami, Eiko Ishida, Atsumi Ide; Nagoya City University: Toshihiko Goto, Nobuyuki Ohte; Shizuoka Medical Center: Asuka Yoshida, Hideaki Kawanaka, Jun Tanabe; St. Marianna University School of Medicine: Keisuke Kida; Komatsu Municipal Hospital: Tomoya Kaneda; Nippon Steel Yawata Memorial Hospital: Shiro Ichihara, Tokushi Koga, Shinichiro Fukushima, Shigeru Kaseda, Yoshie Haga; Oji General Hospital: Hitoshi Oiwa, Katsuhisa Ishii, Tomoaki Matsumoto, Daisuke Yoshida, Noburo Kato; Kitamurayama Hospital: Asuka Yoshida; Komaki City Hospital: Taizo Kondo, Katsuhiro Kawaguchi, Akinori Sawamura.

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Usefulness of Overlapping of the E and A Waves of the Transmitral Flow as a Predictor of Responders to Cardiac Resynchronization Therapy

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Atrioventricular (AV) dyssynchrony as well as ventricular-ventricular dyssynchrony plays an important role in the selection of candidates for cardiac resynchronization therapy (CRT), but no method for assessing the AV dyssynchrony has been established. The aim of this study was to investigate whether the degree of overlap of the E and A waves can predict response to CRT. The study subjects were 48 consecutive patients maintaining sinus rhythm and intrinsic AV conduction who underwent de novo dual-chamber CRT device implantation. CRT responders were defined as those with reductions in left ventricular end-systolic volume >15% at 6 months after CRT device implantations. Twenty-three patients (48%) were CRT responders. In a multivariate analysis, the overlap ratio of the E and A waves was the only independent predictor of response to CRT (odds ratio 1.03, 95% confidence interval 1.01 to 1.06, p = 0.01). Using a cut-off value of 33%, patients with overlap ratios of the E and A waves ≥33% had a significantly higher rate of response to CRT than those with ratios <33% (73% vs 27%, p = 0.002). In conclusion, the overlap ratio of the E and A waves before CRT device implantation may predict CRT response. This simple method may be helpful in evaluating dyssynchrony in patients, particularly with severe reduced left ventricular wall motion, because this method does not require any wall motion analysis. **(Am J Cardiol 2013;111:1613–1618)**

One of the reasons for a lack of a hemodynamic and functional improvement obtained with cardiac resynchronization therapy (CRT) is that the assessment of atrioventricular (AV) dyssynchrony as well as ventricular-ventricular dyssynchrony before CRT device implantation has been controversial. Left ventricular (LV) diastolic filling time measured by transmitral flow for the cardiac cycle length (DFT/RR) has previously been proposed as a parameter of AV dyssynchrony before CRT device implantation.[1] However, this parameter was not sufficient for predicting CRT response in large clinical trials.[2,3] In this study, we focused on the degree of overlap of the E and A waves of transmitral flow before CRT device implantation because timely atrial contraction would be desirable, especially in patients with heart failure and reduced LV ejection fractions (LVEFs). We hypothesized that patients with more overlap of the E and A waves of transmitral flow might be better CRT candidates, and we retrospectively investigated predictors of response to CRT.

Methods

Patients were selected for CRT device implantations according to current guidelines and criteria: (1) severe heart failure (New York Heart Association functional class III or IV) despite optimal medical treatment, (2) an LVEF <35%, and (3) prolonged QRS duration (>120 ms). Of 80 consecutive patients who underwent de novo dual-chamber CRT device implantations at 2 institutions from June 2007 to June 2012, patients with external LV assist devices (n = 4), acquired second- or third-degree AV block (n = 7), persistent atrial tachycardia and/or atrial fibrillation (n = 12), and upgraded pacemakers from right ventricular apical pacing (n = 5) and those without follow-up data (n = 4) were excluded from this study. Ultimately, 48 patients maintained in sinus rhythm and with intrinsic AV conduction were retrospectively analyzed. The study protocol conformed to the Declaration of Helsinki and was accepted by each hospital's ethics committee. Written informed consent was obtained from all patients. All patients underwent baseline evaluations and echocardiographic examinations, including evaluations of dyssynchrony before and 6 months after CRT.

Before hospital discharge, optimization of the AV and ventricular-ventricular intervals was performed by echocardiography or an intracardiac electrocardiographically guided timing cycle optimization algorithm.[4–7] Echocardiographic images were all obtained before CRT device implantation and 6 months after implantation. LV volumes

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See page 1617 for disclosure information.

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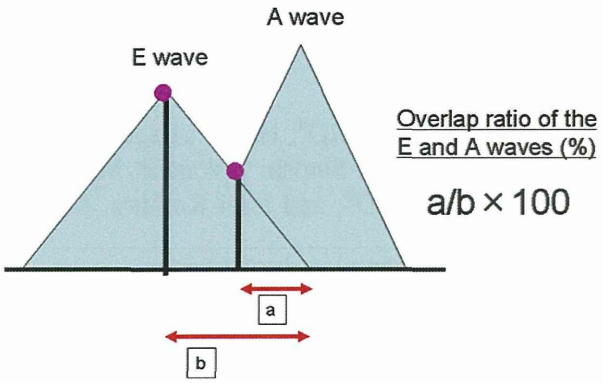

Figure 1. Overlap ratio of the E and A waves. The overlap ratio of the E and A waves is measured as follows: 'a' is the interval between the point of the intersection of the E and A waves and the termination of the E wave, while 'b' is the interval between the peak of the E wave and the termination of the E waves. The overlap ratio of the E and A waves is calculated as (a/b) × 100%. When the E and A waves are completely separated, the overlap ratio of the E and A waves is 0%. When the E and A waves are totally fused, the overlap ratio of the E and A waves is 100%.

were determined using the method previously reported.[8] The grade of mitral regurgitation was assessed according to the guidelines of the American Society of Echocardiography.[9] We calculated the overlap ratio of the E and A waves. This overlap ratio was defined as in Figure 1. In Figure 1, 'a' is the interval between a point of intersection of the E and A waves and the termination of the E wave, while 'b' is the interval between the peak of the E wave and the termination of the E wave. The overlap ratio of the E and A waves was calculated as (a/b) × 100%. When the E and A waves were completely separated, the overlap ratio of the E and A waves was 0%. When the E and A waves were totally fused, the overlap ratio was 100%. We determined the level of intraventricular and interventricular mechanical dyssynchrony with using M-mode echocardiography and tissue Doppler imaging. A septal-posterior wall motion delay obtained on M-mode imaging in the parasternal long-axis view of ≥130 ms[10] or the opposing wall delay between the anteroseptal-to-posterior wall or the septal-to-lateral wall of ≥65 ms was defined as intraventricular mechanical dyssynchrony.[11] Interventricular electromechanical delay was the difference between the LV pre-ejection period and the right ventricular pre-ejection period. An interventricular electromechanical delay of ≥40 ms was defined as interventricular dyssynchrony.[1] A reduction in the LV end-systolic volume of >15% at 6 months after CRT was used as an objective measure of response to CRT in this study.[2,3]

Continuous variables are expressed as mean ± SD. Factors were determined using chi-square tests, and between-group comparisons were made using Mann-Whitney U tests for continuous variables and Fisher's exact tests for dichotomous variables. Only variables with p values <0.05 on univariate analysis were entered into a multivariate logistic regression analysis to identify independent factors of CRT response. A p value <0.05 was considered statistically significant. Receiver-operating characteristic curves were generated, and the area under the curve was determined as a measure of the ability to predict a positive response at any cut-off value. JMP version 9.0 (SAS Institute Inc., Cary, North Carolina) was used for all statistical tests.

Table 1
Baseline characteristics before cardiac resynchronization therapy device implantation

Variable	Overall (n = 48)	Responders (n = 23)	Nonresponders (n = 25)	p Value
Age (yrs)	59 ± 14	64 ± 13	55 ± 14	0.035
Men	34 (71%)	14 (61%)	20 (80%)	0.15
CRT defibrillator	46 (96%)	21 (91%)	25 (100%)	0.13
New York Heart Association class III/IV	36/12	20/3	16/9	0.067
Nonischemic cardiomyopathy	37 (77%)	18 (78%)	19 (76%)	0.85
Heart rate (beats/min)	75 ± 15	74 ± 15	76 ± 15	0.58
PQ interval (ms)	177 ± 40	173 ± 35	180 ± 45	0.56
QRS duration (ms)	147 ± 31	145 ± 27	150 ± 35	0.56
Left bundle branch block	16 (33%)	11 (48%)	5 (20%)	0.048
B-type natriuretic peptide (pg/ml)	389 ± 326	401 ± 409	380 ± 244	0.83
Medications				
β blockers	47 (98%)	22 (96%)	25 (100%)	0.29
Angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers	37 (77%)	19 (83%)	18 (72%)	0.38
Spironolactone	32 (67%)	16 (70%)	16 (64%)	0.68
Diuretics	41 (85%)	17 (74%)	24 (96%)	0.030
Amiodarone	17 (35%)	7 (30%)	10 (40%)	0.48
Digoxin	8 (17%)	4 (17%)	4 (16%)	0.89
Intravenous inotropic agents	10 (21%)	2 (9%)	8 (32%)	0.047

Data are expressed as mean ± SD or as number (percentage).

Results

Patient characteristics are listed in Table 1. β blockers were administered in 47 patients: carvedilol (average dose 8.5 ± 6 mg) in 42 patients, bisoprolol (2.8 ± 0.3 mg) in 2 patients, metoprolol (40 ± 20 mg) in 2 patients, and atenolol (12.5 mg) in 1 patient. The various analyses of the echocardiographic measurements are listed in Table 2. At 6-month follow-up, 23 patients (48%) were CRT responders. Three patients in the nonresponder group experienced progression to persistent atrial fibrillation, whereas all patients in the responder group maintained sinus rhythm. The 2 groups were generally comparable in terms of baseline demographic, clinical, and echocardiographic characteristics (Tables 1 and 2). The overlap ratio of the E and A waves was higher in the responder group than in the nonresponder group (44 ± 34% vs 19 ± 23%, p = 0.006). New York Heart Association functional class and electrocardiographic and echocardiographic parameters 6 months after CRT device implantation are listed in Table 3. Significant reductions in heart rate were more frequently observed in the responder group than in the nonresponder group (67 ± 10 vs 76 ± 10 beats/min, p = 0.004), although the incidence of patients increasing the doses of β blockers was similar between the responder group and the nonresponder group

Table 2
Echocardiographic parameters before cardiac resynchronization therapy device implantation

Variable	Overall (n = 48)	Responders (n = 23)	Nonresponders (n = 25)	p Value
LVEF (%)	26 ± 7	28 ± 6	23 ± 8	0.04
LV end-diastolic volume (ml)	247 ± 88	239 ± 78	254 ± 97	0.56
LV end-systolic volume (ml)	184 ± 82	173 ± 66	195 ± 94	0.37
Left atrial dimension (mm)	46 ± 8	45 ± 8	47 ± 7	0.45
Mitral regurgitation grade ≥II	28 (58%)	13 (57%)	15 (60%)	0.81
Deceleration time of the E wave (ms)	182 ± 64	190 ± 49	173 ± 75	0.35
Tei index	0.56 ± 0.15	0.56 ± 0.15	0.56 ± 0.16	0.97
DFT/RR	0.47 ± 0.07	0.47 ± 0.07	0.46 ± 0.07	0.87
DFT/RR <0.4	9 (19%)	4 (17%)	5 (20%)	0.82
Overlap ratio of the E and A waves (%)	30 ± 31	44 ± 34	19 ± 23	0.006
Septal posterior wall motion delay >130 ms	20/33 (61%)	13/19 (68%)	7/14 (50%)	0.28
Interventricular mechanical delay >40 ms	14/36 (39%)	9/20 (45%)	5/16 (31%)	0.40
Ts (anteroseptal-posterior, septal-lateral) >65 ms	14/27 (52%)	7/15 (47%)	7/12 (58%)	0.55

Data are expressed as mean ± SD or as number (percentage).
Ts = the time to peak myocardial systolic velocity during the ejection phase.

Table 3
Exercise tolerance and electrocardiographic and echocardiographic parameters at 6 months after cardiac resynchronization therapy device implantation

Variable	Overall (n = 48)	Responders (n = 23)	Nonresponders (n = 25)	p Value
New York Heart Association class I/II/III/IV	6/21/14/7	6/14/3/0	0/7/11/7	0.002
Heart rate (beats/min)	72 ± 11	67 ± 10	76 ± 10	0.004
PQ interval (ms)	158 ± 47	139 ± 30	173 ± 53	0.01
QRS duration (ms)	141 ± 22	141 ± 23	142 ± 22	0.95
B-type natriuretic peptide (pg/ml)	324 ± 361	135 ± 129	505 ± 418	0.0003
Echocardiographic parameters				
LVEF (%)	31 ± 12	40 ± 9	22 ± 6	0.0001
Deceleration time of the E wave (ms)	185 ± 66	202 ± 52	170 ± 75	0.11
DFT/RR	0.48 ± 0.08	0.50 ± 0.07	0.46 ± 0.08	0.08
Overlap ratio of the E and A waves (%)	13 ± 23	10 ± 16	16 ± 28	0.36

Data are expressed as mean ± SD or as numbers.

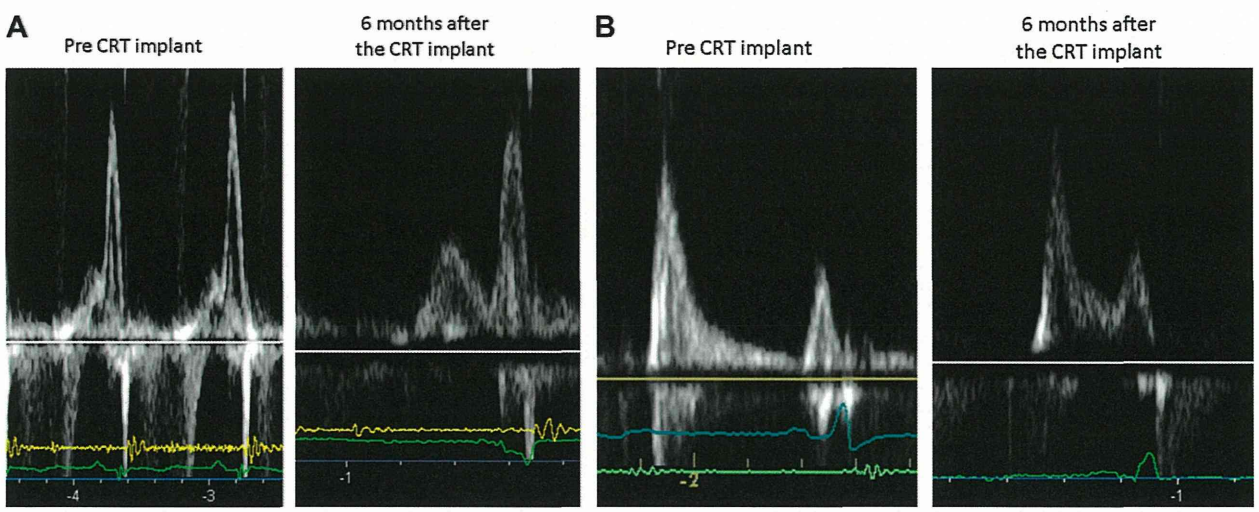

Figure 2. Representative examples of a responder and a nonresponder. *(A)* Representative patient from the responder group. The overlap ratio of the E and A waves before CRT device implantation was 80%. After CRT device implantation, this ratio improved to 20%. *(B)* Representative patient from the nonresponder group. The overlap ratio of the E and A waves before CRT device implantation was 0%. After CRT device implantation, this ratio was also 0%.

(39% vs 36%, p = NS). New York Heart Association functional class improved in 91% of the responders and only 40% of the nonresponders (p = 0.0002). Representative cases in the 2 groups are shown in Figure 2.

On multivariate logistic regression analysis, the overlap ratio of the E and A waves (odds ratio 1.03, 95% confidence interval 1.01 to 1.06, p = 0.01) was an independent predictor of response to CRT. On the basis of the receiver-operating

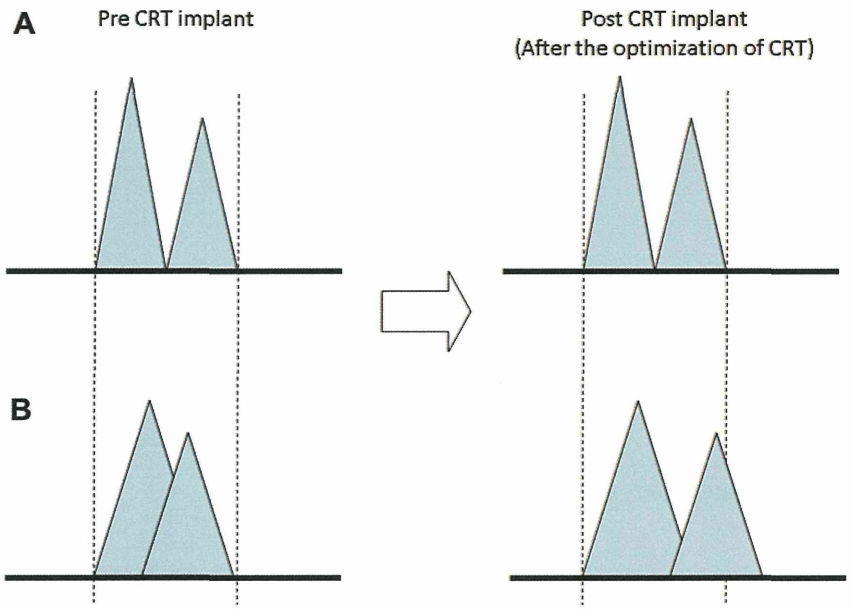

Figure 3. Although the DFT/RR ratio is the same, the DFT/RR ratio alone cannot distinguish between the following patients. *(A)* A patient in whom the E and A waves of transmitral flow are separated. *(B)* A patient in whom the E and A waves of transmitral flow are overlapped. After optimization of CRT, extending the diastolic filling time would be desirable in the latter patient (*B*), but there is little possibility of extending the diastolic filling time in the former patient (*A*).

characteristic curve analysis, the overlap ratio of the E and A waves of transmitral flow achieved an area under the curve of 0.70 ($p = 0.01$) for the ability to predict CRT response, although DFT/RR was not statistically significant. An overlap ratio of the E and A waves of $\geq$33% had optimal sensitivity (68%) and specificity (76%) for predicting responders to CRT. Using a cut-off value of 33%, patients with overlap ratios of the E and A waves of $\geq$33% had a significantly higher response rate than those with overlap ratios of the E and A waves of <33% (73% vs 27%, $p = 0.002$). This cut-off value applied to 10 patients (21%) of CRT super-responders, defined as having significant reductions in LV end-systolic volume of >30%. Patients with overlap ratios of the E and A waves of $\geq$33% had a significantly higher rate of super-response than those with overlap ratios of the E and A waves of <33% (36% vs 8%, $p = 0.01$). Twenty-two patients had overlap ratios of the E and A waves $\geq$33%, and 26 patients did not. DFT/RR was significantly smaller (0.44 ± 0.06 vs 0.49 ± 0.08, $p = 0.008$), and left bundle branch block morphology was significantly more frequently observed in patients with overlap ratios of the E and A waves of $\geq$33% than in those with ratios <33% (64% vs 8%, $p < 0.0001$), while the other baseline and echocardiographic parameters were similar between the groups.

In our study, 17 patients (35%) had LVEFs $\geq$30%, and 31 (65%) had LVEFs <30%. Among patients with LVEFs $\geq$30%, there was a tendency toward a difference but no significant difference in the response rate between patients with overlap ratios of the E and A waves of $\geq$33% and those without (83% vs 37%, $p = 0.06$). However, among patients with LVEFs <30%, those with overlap ratios of the E and A waves of $\geq$33% had a significantly greater number of CRT responders than those with ratios <33% (69% vs 20%, $p = 0.006$).

Discussion

Our results demonstrate that determining the overlap ratio of the E and A waves of transmitral flow before CRT device implantation can be a simple tool for predicting response to CRT in patients with chronic heart failure. The overlap ratio of the E and A waves was higher in the responder group than in the nonresponder group, while DFT/RR and even the other conventional parameters for the prediction of response did not differ between the groups. A multiple regression analysis showed that this overlap ratio was an independent predictor of CRT response after an adjustment of the parameters showing significant differences between the responder and nonresponder groups. This overlap ratio was also a factor for predicting CRT super-response. Moreover, even among patients with low LVEFs, those with higher overlap ratios included more responders than those with lower ratios.

The evidence that the overlap of the E and A waves of transmitral flow is superior to DFT/RR for predicting CRT response can be supported by the limitation of DFT/RR for examining AV dyssynchrony. DFT/RR has been previously proposed as a parameter of AV dyssynchrony,[1] but its usefulness remains controversial.[2,3] One of the reasons is that DFT/RR cannot distinguish between a separation and overlap (Figure 3) of the E and A waves. The former case would not have any beneficial effects, because there is little possibility of extending the diastolic filling time by optimization of the CRT device, but the latter case might have beneficial effects from optimization. In fact, DFT/RR