



Original article

An elevated ratio of early to late diastolic filling velocity recovers after heart transplantation in a time-dependent manner

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ABSTRACT

Background: Several groups have reported that an elevated ratio of early (E) to late (A) diastolic filling velocities is observed in patients after heart transplantation. However, the mechanism has not been fully analyzed.

Methods: Serial echocardiography and hemodynamic study were performed in 16 patients who had received heart transplantation and had no evidence of rejection during 1 month after the operation.

Results: On Day 1 after the surgery, E/A ratio was higher and peak velocity of A wave was lower than normal range among the patients after heart transplantation. E/A ratio and peak velocity of A wave gradually normalized during 1 month after the surgery. Meanwhile, early mitral annular velocity and pulmonary capillary wedge pressure remained within normal range during the study period.

Conclusions: Longer ischemic time during heart transplantation procedure may cause atrial stunning, but it appears to recover within 1 month. We have to be alert to misinterpretation of this “pseudo-normal” mitral inflow pattern early after transplantation.

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Introduction

An elevated ratio of early (E) to late (A) transmitral filling velocity, consistently with a “restrictive” physiology, is typically seen in the advanced stage of left ventricular (LV) diastolic dysfunction among heart failure patients with reduced ejection fraction (EF) [1]. In recipients who received heart transplantation (HTx), several investigators have reported a possible association between diastolic dysfunction of LV and acute cellular rejection [2,3]. Various Doppler echocardiographic indices of LV diastolic function have been proposed for noninvasive screening methods for allograft rejection. Among them, an elevated E/A ratio has been most

commonly reported as a marker to detect acute rejection [4–6], though its usefulness remains controversial [7].

On the other hand, a transmitral inflow pattern also provides insights into left atrial (LA) mechanical function, and decreases in peak velocity of transmitral A wave may be a consequence of attenuated contractility of LA [8]. In fact, a transiently elevated E/A ratio has been observed after conversion of atrial fibrillation into sinus rhythm [9], which usually normalizes after conversion because of the delayed and time-dependent recovery of atrial function [10].

Pascale et al. recently reported that an elevated E/A ratio was observed in recipients who had received standard HTx procedure [11]. They attributed the filling pattern to impaired LA function after surgery, since they did not observe any other evidence for diastolic dysfunction in the transplanted LV. However, to our best knowledge, the time course of E/A ratio after HTx has not been examined thus far. Therefore, the aim of this study was to analyze the time course of various parameters that related to cardiac function during 1 month after HTx.

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Materials and methods

Patient population

We included 21 consecutive recipients, who had received HTx between June 2006 and September 2011 and had been followed for at least 1 month at the University of Tokyo Hospital. Three recipients were excluded because of data insufficiency and two other patients were excluded because they had acute cellular rejection within 1 month after HTx. We finally enrolled 16 HTx recipients in this study. The institutional protocol for the monitoring of rejection with serial endomyocardial biopsy and hemodynamic measurement routinely begins 7 days after transplantation and then weekly in the first month. All patients had undergone standard procedure of HTx (1 patient with Lower–Shumway procedure [12], and the other 15 patients with modified bicaval anastomosis technique [13]) and were treated with a standard immunosuppressive regimen including one of calcineurin inhibitors, mycophenolate mophetil, and low dose prednisolone. Written informed consent was obtained from all patients and/or family members before HTx. The study protocol was approved by the Ethics Committee of Graduate School of Medicine, the University of Tokyo [application number 779 (1)].

Echocardiographic examination

Transthoracic echocardiography was performed during 1 month after HTx. Mitral diastolic flow velocities were recorded by pulse-wave Doppler scanning from the apical four-chamber view with the sample volume positioned at the mitral valvular leaflet tips, and the peak Doppler velocity of early and late diastolic flow as well as deceleration time (DcT) were measured and the E/A ratio was calculated. Mitral annular tissue Doppler image measurements were performed from the apical four-chamber view with the sample volume positioned at the lateral mitral annulus, and the peak early diastolic mitral annular motion velocity (e') was measured.

Statistical analysis

Each variable obtained through routine echocardiography of 1 post-operative week (POW), 2 POW, and 4 POW was

Table 1
Preoperative baseline characteristics.

	N = 16
Age, years	41.4 (20–59)
Age of donor, years	47.2 (19–64)
Male, n (%)	12 (75.0)
Male of donor, n (%)	9 (56.3)
Body height, cm	166.9 ± 8.2
Body weight, kg	55.8 ± 10.0
Body surface area, m ²	1.62 ± 0.18
Total ischemic time, min	242.4 ± 34.8

Ages of recipient and donor are shown as mean and range.

compared with that of Day 1 after the operation (0 POW) by using a Dunnett's post hoc test when a repeated measure analysis of variance approved overall significance. Unless otherwise specified, all data were expressed as mean ± standard deviation. Probability was 2-tailed, with $p < 0.05$ regarded as statistically significant. All statistical analysis was calculated with PASW Statistics 18 (SPSS Inc., Chicago, IL, USA).

Results

Patients' baseline characteristics

We performed serial echocardiography in 16 patients who had received HTx. The mean age of donor hearts was 47.2 ± 14.7 years (ranged between 44 and 64 years), and the mean age of recipients was 41.4 ± 11.7 years (ranged between 20 and 59 years) (Table 1). Total ischemic time of donor hearts was 242.4 ± 34.8 min.

Analysis of the variables related to the LV performance

Fig. 1 depicts values of peak E wave velocity and peak A wave velocity of the patients who received HTx. Peak E wave velocity remained within the normal range during 1 month after HTx. Peak A wave velocity was significantly smaller on the Day 1 after the surgery and gradually normalized in a time-dependent manner within 1 month ($p < 0.01$). E/A ratio was higher on Day 1 after the operation but reduced in a time-dependent manner ($p < 0.01$) and normalized at 1 month after the operation (Fig. 2A). Pulmonary

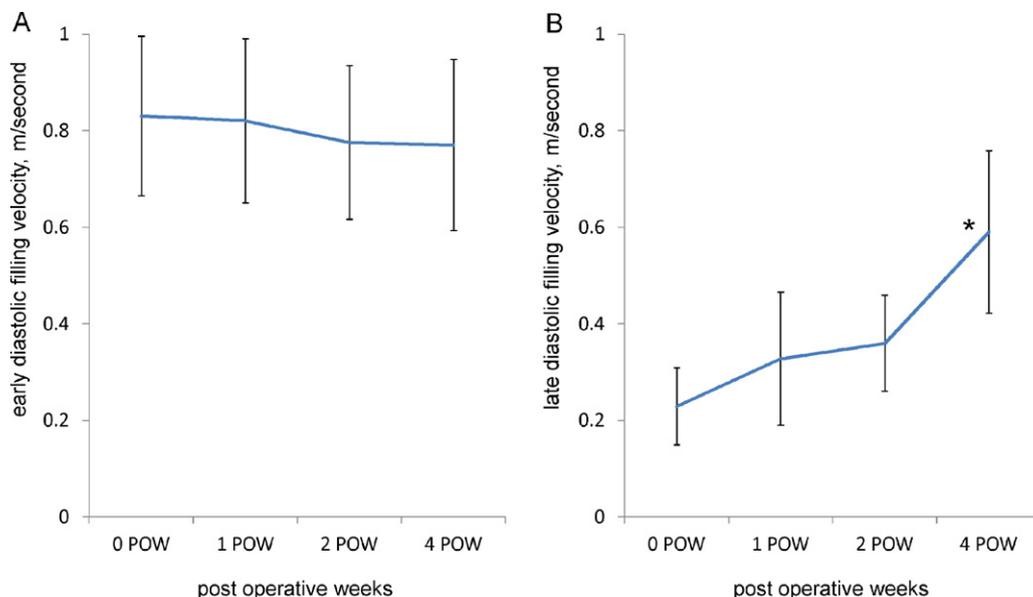


Fig. 1. Early diastolic filling velocity (A) and late diastolic filling velocity (B) of the patients who received heart transplantation. POW, post-operative week. * $p < 0.01$ versus 0 POW.

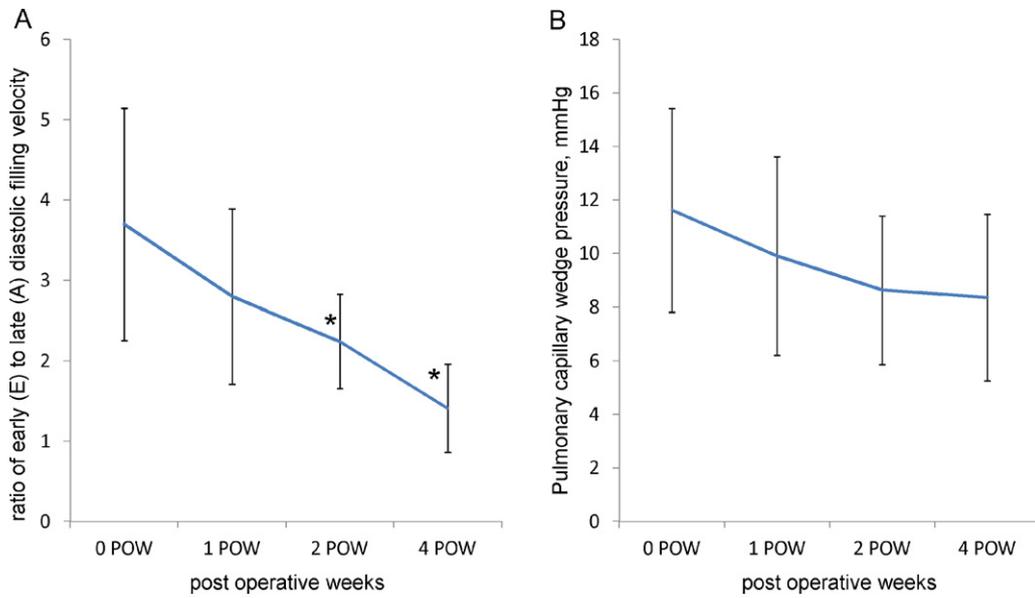


Fig. 2. Ratio of early (E) to late (A) diastolic filling velocity (A) and pulmonary capillary wedge pressure (B) of the patients who received heart transplantation. POW, post-operative week. * $p < 0.01$ versus 0 POW.

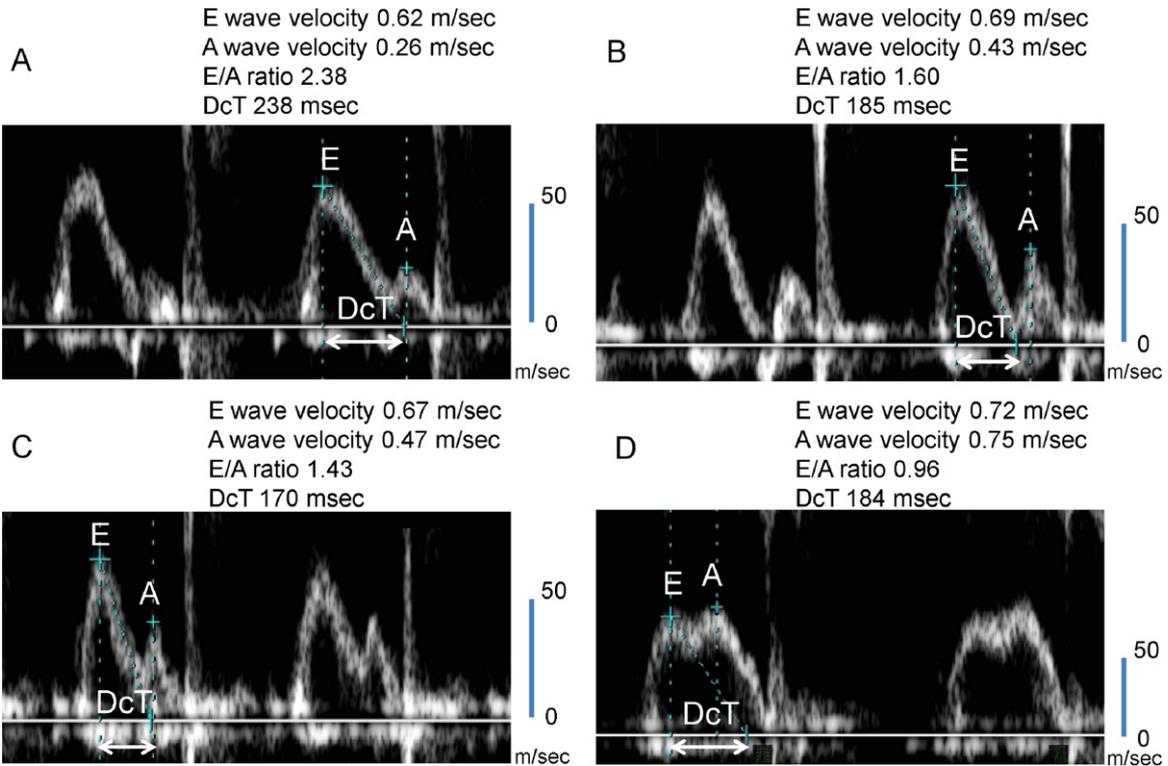


Fig. 3. Representative serial recordings of transmitral flow velocity curves in the patients on Day 1 (A), 1 week (B), 2 weeks (C), and 4 weeks (D) after heart transplantation. DcT, deceleration time.

capillary wedge pressure remained within the normal range during the study period (Fig. 2B). Representative serial recordings of transmitral flow velocity curves in the patients after HTx are shown in Fig. 3, in which peak A wave velocity gradually increased in a time-dependent manner. DcT, E/e' ratio, or peak e' wave velocity did not significantly differ during the study period (Table 2). Fig. 4 shows individual peak e' wave velocity obtained from the patients aged 45 and 54 years and those of the patients aged between 55 and 64 years. Cutoff lines indicating LV diastolic dysfunction were also drawn [14]. As shown in Fig. 4, peak e' wave velocity did not

consistently indicate diastolic dysfunction in any patients. None of the echocardiographic data of the one patient who received Lower-Shumway procedure were different from the data of those who received modified bicaval method.

Discussion

We demonstrated in this study that an elevated E/A ratio normalized during 1 month after HTx, which might be attributable to the time-dependent recovery of atrial contractility from stunning.

Table 2
Echocardiographic parameters and hemodynamic parameters.

	0 POW	1 POW	2 POW	4 POW
Echocardiographic parameters				
Ejection fraction, %	65.8 ± 3.2	66.9 ± 5.8	68.6 ± 4.7	69.2 ± 3.4
Peak E velocity, m/s	0.83 ± 0.20	0.82 ± 0.20	0.78 ± 0.16	0.77 ± 0.18
Peak A velocity, m/s	0.23 ± 0.08	0.33 ± 0.14	0.36 ± 0.10	0.59 ± 0.17*
Deceleration time, s	191.1 ± 33.4	173.3 ± 26.5	173.3 ± 19.2	167.1 ± 15.0
E/A ratio	3.70 ± 1.44	2.80 ± 1.09	2.24 ± 0.58†	1.41 ± 0.55*
Peak e' velocity, cm/s	10.46 ± 2.09	9.67 ± 1.45	10.05 ± 2.02	10.10 ± 1.57
E/e' ratio	8.25 ± 2.72	9.03 ± 2.97	8.32 ± 1.94	7.80 ± 1.92
Hemodynamic parameters				
Mean RA pressure, mmHg	8.0 ± 4.6	6.1 ± 3.2	5.6 ± 3.8	4.5 ± 3.3
RVsP, mmHg	30.2 ± 7.0	31.8 ± 8.5	30.7 ± 7.3	28.3 ± 7.7
PCWP, mmHg	11.7 ± 3.3	9.2 ± 5.0	7.5 ± 2.3	7.2 ± 1.3
Cardiac index, L/min/m ²	2.38 ± 0.43	2.37 ± 0.37	2.30 ± 0.32	2.49 ± 0.51
BNP, pg/mL	–	511.3 ± 304.0	393.1 ± 187.6	263.5 ± 128.9†

POW, postoperative week; RA, right atrial; RVsP, right ventricular systolic pressure; PCWP, pulmonary capillary wedge pressure; BNP, B-type natriuretic peptide.

* $p < 0.01$ versus 0 POW.

† $p < 0.05$ versus 1 POW.

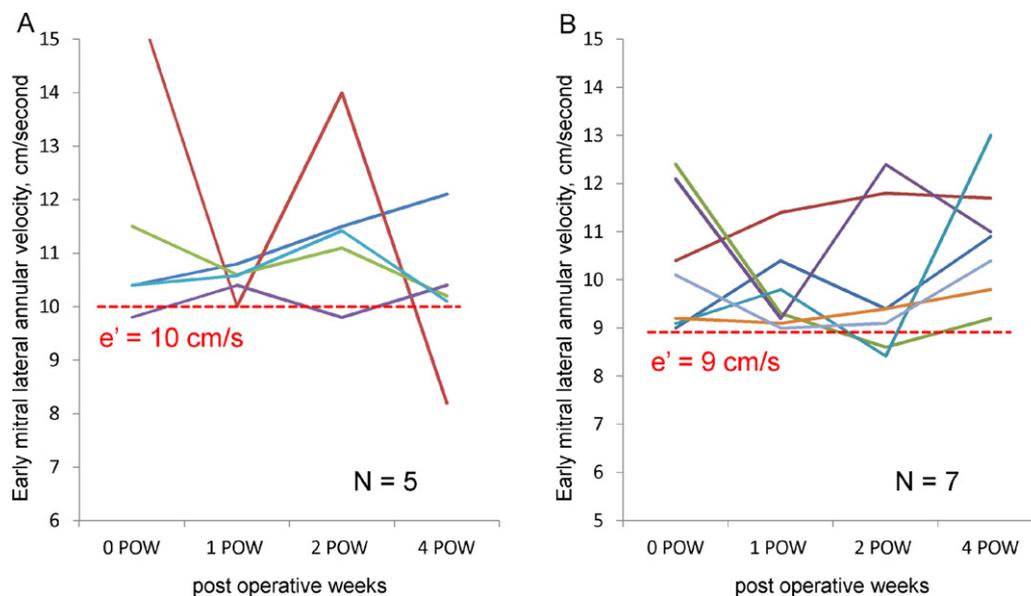


Fig. 4. Early mitral lateral annulus velocity (e') of the patients aged between 45 and 54 years (A) and the patients aged between 55 and 64 years (B). POW, post-operative week.

Any observations on E/e' ratio, peak e' wave velocity, or PCWP did not support underlying LV diastolic dysfunction early after HTx. The preoperative condition of donor hearts was considerably preserved through our scrupulous screening, although hemodynamic and echocardiographic data about diastolic dysfunction in donor hearts were not fully available.

We excluded two recipients who had acute cellular rejection during the study period. Acute cellular rejection is occasionally associated with diastolic dysfunction [2,15], and several indices obtained from echocardiographic examination such as elevated E/e' ratio [6], shorter DcT [4], and higher E/A ratio [5] have been reported to have a correlation with cardiac rejection, although a systematic review has argued that no single diastolic index by echocardiography can be a good screening test in the prediction of cellular rejection after HTx [7].

The mitral inflow pattern of restrictive physiology is characterized by increased filling pressure and shortened DcT especially in patients with reduced EF, but at the same time myocardial relaxation is almost always abnormal with markedly decreased mitral

annular e' velocity, which is less preload dependent [16]. In the VALIDD study, diastolic dysfunction was defined as e' wave velocity < 10 cm/s for patients aged between 45 and 54 years, and < 9 cm/s for patients aged between 55 and 65 years [14]. According to the criteria, most peak e' wave velocities in our patients remained above the cutoff line of LV diastolic dysfunction during 1 month after HTx (see Fig. 4). The result suggests that there was no evidence of LV diastolic dysfunction among the recipients aged over 45 years perioperatively.

Elevated E/e' ratio has been known as an important marker of LV diastolic dysfunction. The American Society of Echocardiography also reported that the E/e' ratio is the most reproducible echocardiographic parameter to estimate pulmonary capillary wedge pressure (PCWP), and lateral E/e' ratio over 12 represents higher LV filling pressure [1]. There was only one patient with lateral E/e' over 12. However, a recent study showed that E/e' ratio cannot necessarily be an alternative index for LV filling pressure such as PCWP [17]. In our observation, PCWP, which was a classical and direct index for LV diastolic dysfunction [18], was not as high as

the level of diastolic dysfunction among all HTx recipients. The results of E/e' ratio, peak e' wave velocity, and PCWP suggest no diastolic dysfunction in our patients who received HTx. Higher levels of B-type natriuretic peptide are another standard marker of diastolic dysfunction [19,20], but the plasma concentrations of B-type natriuretic peptide generally elevate above normal range until 3 weeks after the cardiac operation despite no obvious cardiac impairment [21], and therefore, cannot be a reliable marker early after HTx.

The American Society of Echocardiography reported that the mitral A wave velocity reflects the LA–LV pressure gradient during late diastole, which is affected by not solely LV relaxation but also LA contractile function [1]. In our study, all recipients underwent Lower–Shumway [12] or modified bicaval anastomosis technique [13], and in both procedures a piece of recipient's LA and an LA–LA anastomosis line were left. Some authors argued that decreased LA contraction after HTx with LA–LA anastomosis was related to the reduced contractility of the resultant recipient's atrium [22] or the asynchronous contraction of the donor and recipient's atrium [23]. In fact, Pascale et al. demonstrated that the higher proportion of the recipient LA cuffs to that of donor heart correlated with decreased A wave velocity, i.e. decreased overall LA contractility [11]. Their candidates who had decreased LA contractility after HTx had over 60% of recipient's LA in overall LA volume. However, we routinely leave only a small piece of recipient's LA in HTx procedure, and recipient's LA may be less influential to overall LA contractility after HTx. In other words, there would be other mechanisms that made LA contractility decreased after HTx in our population.

Considering the time-dependent reversibility of A-wave velocity in our study, a major cause of transiently impaired atrial function may be an atrial stunning due to exposure to several hours of ischemia. Braunwald et al. for the first time defined myocardial stunning as a phenomenon that an ischemic insult not of sufficient severity or duration to produce myocardial necrosis would interfere with normal myocardial function for prolonged periods even after reperfusion [24]. Some studies also reported that decreased peak A-wave velocity due to atrial stunning in patients with atrial fibrillation recovered time-dependently after conversion to sinus rhythm over 1 month [9,10]. Therefore, the elevated E/A ratio after HTx may be the result of the impaired contractile function of LA.

It is well known that 20% of cerebrovascular complications, the majority of which was ischemic stroke, occurred within the first two weeks after HTx [25,26]. This observation may also advocate a concept of transient LA stunning early after HTx. In fact, "moyamoya echo" indicating atrial stunning was observed in 6 cases especially within 1 week after HTx. Fortunately, there was no thrombosis in all our recipients after HTx thanks to the administration of antiplatelet agent. Careful observation by transthoracic echocardiography or transesophageal echocardiography would be recommended for the recipients with severely decreased A wave amplitude after HTx in order to detect atrial thrombus precociously.

We acknowledge that our study has several limitations. This study was conducted in a single center, and consequently included a limited number of patients because of a shortage of donor hearts in Japan. We expect the number of HTx will increase due to the amendment of organ transplantation law in July 2010 and strengthen our analyses. Also, blood flow during atrial contraction moves largely back into pulmonary veins in the case of LV diastolic dysfunction. Although several other indices including peak e' wave velocities and PCWP did not consistently suggest LV diastolic dysfunction, we have to admit that we lack data about pulmonary venous flow.

In conclusion, an elevated E/A ratio appears soon after HTx but normalizes within a month. This knowledge would be useful to avoid misinterpretation of acute cellular rejection or actual

diastolic dysfunction especially in the early postoperative period. The elevated E/A ratio may be attributable to atrial stunning caused by long ischemic time during HTx procedure.

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References

- [1] Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, Waggoner AD, Flachskampf FA, Pellikka PA, Evangelista A. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *J Am Soc Echocardiogr* 2009;22:107–33.
- [2] Skowronski EW, Epstein M, Ota D, Hoagland PM, Gordon JB, Adamson RM, McDaniel M, Peterson KL, Smith Jr SC, Jaski BE. Right and left ventricular function after cardiac transplantation. Changes during and after rejection. *Circulation* 1991;84:2409–17.
- [3] Amende I, Simon R, Seegers A, Daniel W, Heublein B, Hetzer R, Haverich A, Hood Jr WP, Lichtlen PR, Schutzenmeister R, Wenzlaff P. Diastolic dysfunction during acute cardiac allograft rejection. *Circulation* 1990;81(2 Suppl.):III66–70.
- [4] Desruennes M, Corcos T, Cabrol A, Gandjbakhch I, Pavie A, Leger P, Eugene M, Bors V, Cabrol C. Doppler echocardiography for the diagnosis of acute cardiac allograft rejection. *J Am Coll Cardiol* 1988;12:63–70.
- [5] Sun JP, Abdalla IA, Asher CR, Greenberg NL, Popovic ZB, Taylor DO, Starling RC, Thomas JD, Garcia MJ. Non-invasive evaluation of orthotopic heart transplant rejection by echocardiography. *J Heart Lung Transplant* 2005;24:160–5.
- [6] Eun LY, Gajarski RJ, Graziano JN, Ensing GJ. Relation of left ventricular diastolic function as measured by echocardiography and pulmonary capillary wedge pressure to rejection in young patients (< or =31 years) after heart transplantation. *Am J Cardiol* 2005;96:857–60.
- [7] Mena C, Wencker D, Krumholz HM, McNamara RL. Detection of heart transplant rejection in adults by echocardiographic diastolic indices: a systematic review of the literature. *J Am Soc Echocardiogr* 2006;19:1295–300.
- [8] Manning WJ, Silverman DI, Katz SE, Douglas PS. Atrial ejection force: a noninvasive assessment of atrial systolic function. *J Am Coll Cardiol* 1993;22:221–5.
- [9] Manning WJ, Leeman DE, Gotch PJ, Come PC. Pulsed Doppler evaluation of atrial mechanical function after electrical cardioversion of atrial fibrillation. *J Am Coll Cardiol* 1989;13:617–23.
- [10] Yamada H, Donal E, Kim YJ, Agler DA, Zhang Y, Greenberg NL, Mazgalev TN, Thomas JD, Grimm RA. The pseudorestrictive pattern of transmitral Doppler flow pattern after conversion of atrial fibrillation to sinus rhythm: is atrial or ventricular dysfunction to blame? *J Am Soc Echocardiogr* 2004;17:813–8.
- [11] Pascale P, Monney P, Jeanrenaud X, Aebischer N, Yerly P, Vogt P, Pruvot E, Schlapfer J. Reduced atrial emptying after orthotopic heart transplantation masquerading as restrictive transmitral Doppler flow pattern? *Echocardiography* 2011;28:168–74.
- [12] Lower RR, Stofer RC, Shumway NE. Homovital transplantation of the heart. *J Thorac Cardiovasc Surg* 1961;41:196–204.
- [13] Kitamura S, Nakatani T, Bando K, Sasako Y, Kobayashi J, Yagihara T. Modification of bicaval anastomosis technique for orthotopic heart transplantation. *Ann Thorac Surg* 2001;72:1405–6.
- [14] Solomon SD, Janardhanan R, Verma A, Bourgoun M, Daley WL, Purkayastha D, Lacourciere Y, Hippler SE, Fields H, Naqvi TZ, Mulvagh SL, Arnold JM, Thomas JD, Zile MR, Aurigemma GP, et al. Effect of angiotensin receptor blockade and antihypertensive drugs on diastolic function in patients with hypertension and diastolic dysfunction: a randomised trial. *Lancet* 2007;369:2079–87.
- [15] Imamura T, Shiga T, Endo M, Inaba T, Maki H, Hatano M, Yao A, Hirata Y, Nagai R. Reversible abnormality of electrocardiogram as a sign of acute cardiac rejection after orthotopic heart transplantation. *JC Case* 2012.
- [16] Sohn DW. Heart failure due to abnormal filling function of the heart. *J Cardiol* 2011;57:148–59.
- [17] Maeder MT, Karapanagiotidis S, Dewar EM, Gamboni SE, Htun N, Kaye DM. Accuracy of Doppler echocardiography to estimate key hemodynamic variables in subjects with normal left ventricular ejection fraction. *J Card Fail* 2011;17:405–12.
- [18] Aurigemma GP, Zile MR, Gaasch WH. Contractile behavior of the left ventricle in diastolic heart failure: with emphasis on regional systolic function. *Circulation* 2006;113:296–304.
- [19] Yu CM, Sanderson JE, Shum IO, Chan S, Yeung LY, Hung YT, Cockram CS, Woo KS. Diastolic dysfunction and natriuretic peptides in systolic heart failure. Higher ANP and BNP levels are associated with the restrictive filling pattern. *Eur Heart J* 1996;17:1694–702.
- [20] Harada M, Hara F, Yamazaki J. Correlation between plasma B-type natriuretic peptide levels and left ventricular diastolic function using color kinetic imaging. *J Cardiol* 2010;56:91–6.

- [21] Morimoto K, Mori T, Ishiguro S, Matsuda N, Hara Y, Kuroda H. Perioperative changes in plasma brain natriuretic peptide concentrations in patients undergoing cardiac surgery. *Surg Today* 1998;28:23–9.
- [22] Cresci S, Goldstein JA, Cardona H, Waggoner AD, Perez JE. Impaired left atrial function after heart transplantation: disparate contribution of donor and recipient atrial components studied on-line with quantitative echocardiography. *J Heart Lung Transplant* 1995;14:647–53.
- [23] Triposkiadis F, Starling RC, Haas GJ, Sparks E, Myerowitz PD, Boudoulas H. Timing of recipient atrial contraction: a major determinant of transmitral diastolic flow in orthotopic cardiac transplantation. *Am Heart J* 1993;126:1175–81.
- [24] Braunwald E, Kloner RA. The stunned myocardium: prolonged, postischemic ventricular dysfunction. *Circulation* 1982;66:1146–9.
- [25] Belvis R, Fabregas JM, Cocho D, Garcia-Bargo MD, Franquet E, Agudo R, Brosa V, Camprecios M, Puig M, Marti-Vilalta JL. Cerebrovascular disease as a complication of cardiac transplantation. *Cerebrovasc Dis* 2005;19:267–71.
- [26] Alejaldre A, Delgado-Mederos R, Santos MA, Marti-Fabregas J. Cerebrovascular complications after heart transplantation. *Curr Cardiol Rev* 2010;6:214–7.