Clin Transplant 2015 DOI: 10.1111/ctr.12587

Elevated resting heart rate in heart transplant recipients: innocent bystander or adverse prognostic indicator?

Wachter SB, McCandless SP, Gilbert EM, Stoddard GJ, Kfoury AG, Reid BB, McKellar SH, Nativi-Nicolau J, Saidi A, Barney J, McCreath L, Koliopoulou A, Wright SE, Fang JC, Stehlik J, Selzman CH, Drakos SG. Elevated resting heart rate in heart transplant recipients: innocent bystander or adverse prognostic indicator?

Abstract: Background: The elevated baseline heart rate (HR) of a heart transplant recipient has previously been considered inconsequential. However, we hypothesized that a resting HR above 100 beats per minute (bpm) may be associated with morbidity and mortality.
Methods: The U.T.A.H. Cardiac Transplant Program studied patients who received a heart transplant between 2000 and 2011. Outpatient HR values for each patient were averaged during the first year post-transplant. The study cohort was divided into two groups: the tachycardic (TC) (HR >100 bpm) and the non-TC group (HR ≤100 bpm) in which mortality, incidence of rejection, and cardiac allograft vasculopathy were compared.
Results: Three hundred and ten patients were included as follows: 73 in the TC and 237 in the non-TC group. The TC group had a higher risk of a 10-yr all-cause mortality ($p = 0.004$) and cardiovascular mortality ($p = 0.044$). After adjustment for donor and recipient characteristics in multivariable logistic regression analysis, the hazard ratio was 3.9, ($p = 0.03$, CI: 1.2–13.2) and 2.6 ($p = 0.02$, CI: 1.2–5.5) for cardiovascular mortality and all-cause mortality, respectively.
Conclusion: Heart transplant recipients with elevated resting HR appear to have higher mortality than those with lower resting HR. Whether pharmacologically lowering the HR would result in better outcomes warrants further investigation.

S. Blake Wachter[a,b], Sean P. McCandless[a], Edward M. Gilbert[a,b], Gregory J. Stoddard[a,b], Abdallah G. Kfoury[b,c], Bruce B. Reid[b,c], Stephen H. McKellar[a,b], Jose Nativi-Nicolau[a,b], Abdulfattah Saidi[a,b], Jacob Barney[a], Lauren McCreath[a], Antigone Koliopoulou[a,b], Spencer E. Wright[a], James C. Fang[a,b], Josef Stehlik[a,b], Craig H. Selzman[a,b] and Stavros G. Drakos[a,b]

[a]School of Medicine, University of Utah, Salt Lake City, UT, USA, [b]UTAH Cardiac Transplant Program, Salt Lake City, UT, USA and [c]Intermountain Heart Institute, Salt Lake City, UT, USA

Key words: all-cause mortality – cardiac allograft vasculopathy – heart rate – heart transplant – multivariable analysis

Corresponding author: Stavros G. Drakos, MD/PhD, Medical Director, Cardiac Mechanical Support Program, University of Utah, 30 North 1900 East, Room 4A100 SOM, Salt Lake City, 84132 UT, USA.
Tel.: +801 585 2340; fax: +801 585 0701;
e-mail: stavros.drakos@hsc.utah.edu

Conflict of interest: None.

Accepted for publication 1 July 2015

Heart rate (HR) can be considered a determinant of health status, with increasing HR being a risk factor of poor outcomes. Levine et al. have documented an inverse semilogarithmic relationship between HR and life expectancy, with a remarkably constant average of $7.3 \pm 5.6 \times 10^8$ heart beats/lifetime, suggesting a finite number of beats the heart can sustain (1). Many studies have shown that an elevated resting HR increases the risk of cardiovascular disease both in the general population and in patients with stable coronary artery disease, independent of other comorbidities (2, 3). Investigators of the Framingham Heart Study identified an elevated resting HR and reduced HR variability as a predictor of all-cause mortality, cardiac events, and the development of hypertension (4, 5). It has further been shown that an increase in HR by 10 beats per minute (bpm) is associated with an increase in the risk of cardiovascular disease, comparable to the increased risk attributed to the diagnosis of hypertension (6).

In heart transplant (HT) recipients, tachycardia is a common finding. The allograft denervation and the absence of the parasympathetic influences

mediated by the vagus nerve lead to an elevated resting HR (7, 8). Despite its high prevalence among HT recipients, the clinical significance of an elevated HR in this specific subgroup of patients is not well understood (9, 10). An inappropriately high HR has been shown to have an increased demand for myocardial oxygen and a decrease in the resting stroke volume and in myocardial perfusion (11, 12). Whether, in the long term, these mechanisms could cause allograft dysfunction has not been established. Similarly, it is unknown whether a reduction in HR after HT would result in beneficial effects on morbidity or mortality. Therefore, we hypothesized that in HT recipients, a sustained HR above 100 bpm may increase the risk of all-cause and cardiovascular mortality.

Methods

We retrospectively studied all adult patients who received an orthotropic HT from the U.T.A.H. Cardiac Transplant Program (University of Utah Health Sciences Center, Intermountain Healthcare and Salt Lake City Veterans Affairs Medical Center) between the years 2000 and 2011. An institutional review board approved of this project. HR recorded at outpatient visits during the first year post-transplant (month 3 to month 12) was averaged for each patient, and the study cohort was divided into two groups: the tachycardia (TC) group with average HR greater than 100 bpm and the non-tachycardia (non-TC) group with average HR less than or equal to 100 bpm. Patients who expired within three months of transplant, who were younger than 18 yr at time of transplant, or who had documented arrhythmias other than sinus tachycardia were excluded.

We further examined all-cause mortality, cardiovascular mortality, incidence of acute rejection, and cardiac allograft vasculopathy (CAV). These patients were evaluated at regular intervals in accordance with the institution's post-transplantation management standards. Further, results from clinical examinations, laboratory tests, echocardiograms, endomyocardial biopsies, right heart catheterizations, and coronary angiograms were also examined. Data related to common comorbidities that may affect HR levels and/or mortality/morbidity including thyroid function and concomitant medications during the first year post-HT were also analyzed.

Baseline continuous variables were expressed as mean $\pm$ standard deviation and categorical variables as frequencies and percentages. Comparisons between the TC and non-TC groups were made using a two-sample *t*-test or chi-square test, as appropriate. For both the TC and the non-TC groups, cumulative freedom from an event rate as a function of time after HT was performed using Kaplan–Meier analysis and compared using a log rank test. A multivariable Cox regression model was used to compare the two groups after controlling for potential confounding variables in the model for the all-cause mortality and cardiovascular mortality outcome models.

To check the linearity assumption of HR, we computed HR quartiles (61.2–87.0, 87.1–93.1, 93.1–99.3, 99.4–117.5) and included the quartiles into the Cox regression model, using the first quartile as the baseline. The hazard ratios were essentially equal to 1.0 for quartiles two and three and not significant (both $p > 0.96$), while the fourth quartile hazard ratio was greater than 2.0 and was significant. This verified that the linearity assumption was not met suggesting HR follows a threshold–response rather than a dose–response relationship with all-cause mortality. Therefore, HR as a binary predictor at the clinically accepted cutoff of 100 was utilized. A two-tailed p-value less than 0.05 for all evaluations was considered significant.

Results

A total of 405 patients received an HT between the years 2000 and 2011; of those, 310 subjects met the study inclusion criteria. 237 patients had an average HR less than or equal to 100 bpm with an average HR of 89 $\pm$ 7.8 bpm; these were assigned to the non-TC group. Seventy-three patients had an average HR more than 100 bpm with an average HR of 107 $\pm$ 4.6 bpm; these were assigned to the TC group. Patient characteristics along with the leading etiologies of heart disease for both groups are listed in Table 1. The average age was 50 $\pm$ 12 and 49 $\pm$ 14 (p=not significant [NS]) years, and the percent male was 81% and 74% (p=NS) in the non-TC group and the TC group, respectively. The leading etiologies for the non-TC and TC groups were coronary artery disease (46%) and idiopathic cardiomyopathy (45%), respectively.

Freedom from all-cause mortality and cardiovascular mortality is shown in Fig. 1. Subjects in the TC group had a higher risk of all-cause mortality ($p = 0.004$, Fig. 1A) and of cardiovascular mortality ($p = 0.044$, Fig. 1B) compared to the non-TC group. The cumulative incidence of non-cardiovascular mortality, acute cellular rejection, and CAV was similar between the two groups (Table 2). Evaluation of long-term effects of tachycardia was documented by analysis of ejection fraction. Beyond one yr, comparison between

Table 1. Patient characteristics

	Non-TC (HR ≤ 100) n = 237	TC (HR > 100) n = 73	p-value
Donor characteristics			
Male	167 (71%)	50 (69%)	NS
CMV mismatch	49 (21%)	14 (19%)	NS
Transplant age (yr)	32 ± 12	24 ± 9	<0.001
Recipient baseline characteristics			
Male	190 (81%)	54 (74%)	NS
Age	50 ± 12	49 ± 14	NS
DM	45 (19%)	17 (23%)	NS
HTN	96 (41%)	28 (38%)	NS
CKD	35 (15%)	10 (14%)	NS
Hypothyroidism	37 (16%)	10 (14%)	NS
HLD	112 (47%)	31 (42%)	NS
CVA	20 (8%)	11 (15%)	NS
BMI	27 ± 5	25 ± 4	0.002
Smoked	115 (50%)	33 (46%)	NS
Recipient etiology			
CAD	46%	41%	NS
Idiopathic CM	41%	45%	NS
Congenital CM	3%	8%	NS
Valvular CM	2%	3%	NS
Other	10%	2%	NS
Recipient outcomes, one yr after transplant			
TSH < 0.3	9 (4%)	5 (7%)	NS
Hgb < 9	31 (13%)	5 (7%)	NS
LDL > 100	67 (28%)	18 (25%)	NS
BB	72 (30%)	12 (16%)	0.02
CCB	72 (30%)	17 (23%)	NS
ACE-I	152 (64%)	50 (68%)	NS
Statin	233 (98%)	68 (93%)	0.02
Levothyroxine	44 (19%)	12 (16%)	NS

All values are the frequency with (%) or mean ± standard deviation. CMV, cytomegalovirus; DM, diabetes mellitus; HTN, hypertension; CKD, chronic kidney disease; HLD, hyperlipidemia; CVA, cerebral vascular accident; BMI, body mass index; CAD, coronary artery disease; CM, cardiomyopathy; TSH, thyroid stimulating hormone; Hgb, hemoglobin; LDL, low density lipoprotein; BB, beta-blocker; CCB, calcium channel blocker; ACE-I, angiotensin-converting enzyme inhibitor; NS, not significant.

TC and the non-TC groups at one, two, three, and five yr were not statically significant (Table 3).

We carried out a multivariable Cox regression analyses that considered a wide range of donor and recipient characteristics. In these models, average HR greater than 100 bpm remained a risk factor for all-cause mortality with a hazard ratio of 2.56 (p = 0.02, CI: 1.19–5.49) and for cardiovascular mortality with a hazards ratio of 3.93 (p = 0.03, CI: 1.17–13.19) as shown in Table 4.

Discussion

Within this retrospective study, we found that HT recipients with an elevated resting HR had a significant increase in all-cause mortality and in cardiovascular mortality, but no significant differences in the development of cardiac rejection or CAV. Designing a study with an inherently variable vital sign such as HR is challenging. We chose to study vital signs collected at routine outpatient visits from month three to month twelve after HT as most patients are stable enough to be seen in outpatient clinic by three months and the HR stabilizes over the first year. We chose to use outpatient clinic visits to avoid hospitalizations where the HR could be expected to be elevated from baseline due to the acute event that lead to the hospitalization.

HT patients often have complex medical problems. Some patients may have higher mortality because of their underlying comorbidities before HT (13). In our study, we found that pre-transplant comorbidities including diabetes mellitus, hypothyroidism, stroke, smoking, and obesity were similar between the two groups. Other medical complications arise from the necessary immunosuppressive therapies, which can cause, for example, renal failure, leukocytopenia, and hypertension (14). The patients in the two groups received comparable post-transplant immunosuppression regimens (data not shown). In our study, we did not find any significant differences between the two groups in allograft rejection, either cellular or antibody mediated.

Other medical conditions besides HT itself can be manifested by tachycardia. The development of atrial fibrillation is relatively rare in the post-HT population. In our study, only two patients had chronic atrial fibrillation documented by electrocardiogram one yr after HT. Anemia or hyperthyroidism can also account for elevated HR; these were found to be comparable between the two study groups. HT recipients often develop systemic hypertension and are frequently started on antihypertensive medications such as calcium channel blockers, angiotensin-converting enzyme inhibitors, and beta-blockers. The non-TC group was prescribed beta-blockers more often compared to the TC group. This could be viewed as a limitation of our study despite the fact that there was no independent effect of the use of beta-blockers in the multivariable regression analysis on mortality and cardiovascular mortality.

In our study, the survival curves overlap early on and showed a difference in mortality later. Early on the similar outcomes between the groups could possibly be explained by comparable postoperative complications and rejection outcomes. Tachycardia-induced cardiomyopathy is an expected complication of patents with long-standing tachycardia and could explain at least partially the difference observed in late outcomes. However, our study did not support this finding in our subject groups. Ejection fractions compared at one, two, three, and

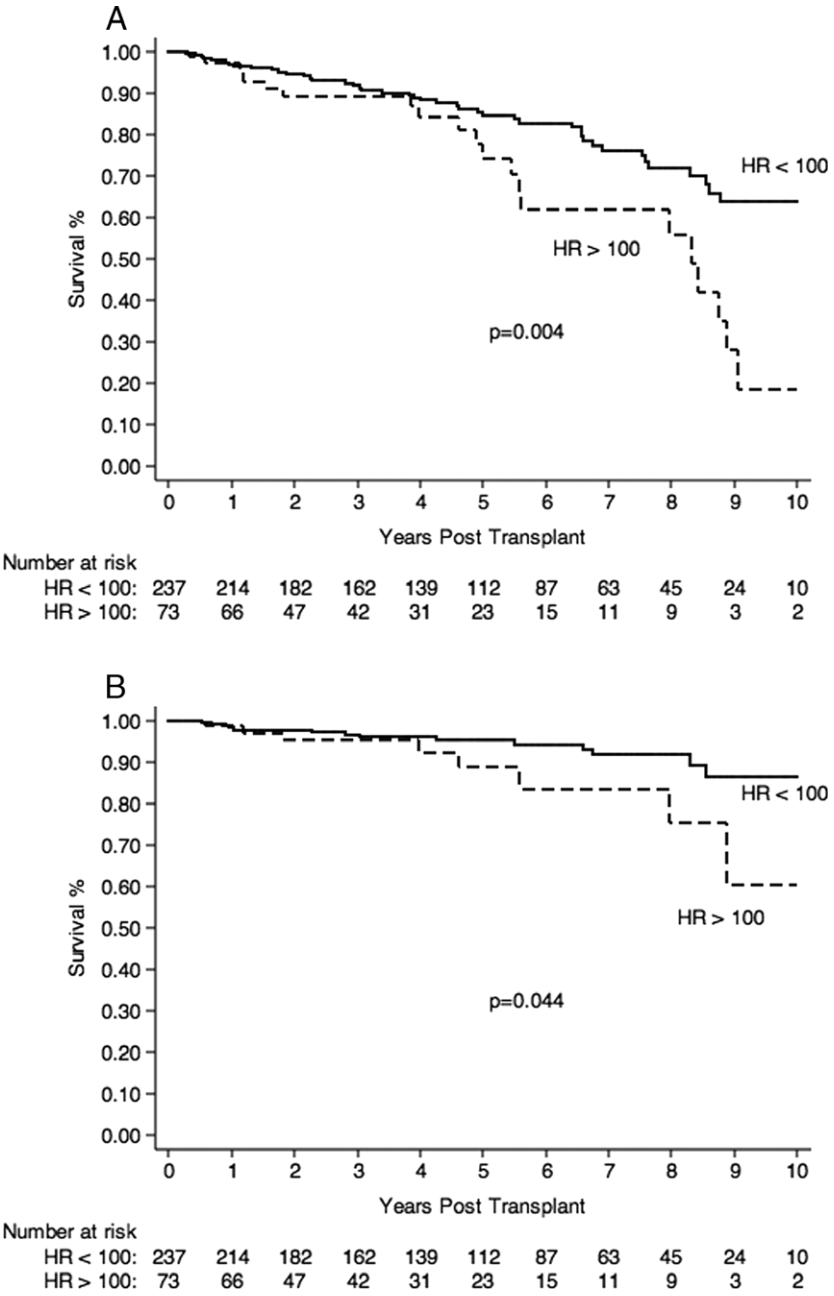

Fig. 1. Kaplan–Meier freedom from all-cause mortality (A) and cardiovascular mortality (B). p-value is from the log rank test.

five yr post-transplant were similar and within normal range of 55–65%. Of note, we did not examine the possible development of diastolic dysfunction, which could explain higher mortality between groups and is a limitation of this study.

In normal subjects, resting HR is predominantly determined by vagal influences (15). Due to the denervation at cardiac transplant of the donor heart, parasympathetic influences on the donor HR are absent and these influences may be present for up to 96 months after HT (16). As a result, tachycardia is common among heart donor and recipients. A mechanism that could account for lower HR in post-transplanted recipients is re-innervation (17). Re-innervation could have other possible benefits such as improved contractile function with exercise that could account for the decreased mortality seen in this study (18).

Ivabradine, a selective and specific inhibitor of the mixed sodium/potassium inward (*If*) current, regarded as one of the most important ionic currents regulating pacemaker activity in the sinoatrial node, has recently been studied in heart disease. Several smaller studies have shown that reduction in HR using ivabradine in patients with stable coronary artery disease, chronic heart failure, or post-HT may improve outcomes, improve diastolic dysfunction, reduce cardiac fibrosis, and

Table 2. Freedom from all-cause mortality, cardiovascular (CV) deaths, non-CV deaths, acute cellular rejection, and cardiac allograft vasculopathy (CAV) at one, three, five, and 10 yr, respectively

	Group	Freedom from all-cause mortality	Freedom from CV death	Freedom from non-CV mortality	Freedom from acute cellular rejection	Freedom from CAV
One-yr	Non-TC	97%	98%	99%	61%	96%
	TC	97%	96%	99%	68%	98%
	p-value	0.92	0.84	0.95	0.29	0.79
Three-yr	Non-TC	92%	97%	95%	50%	94%
	TC	89%	95%	94%	59%	93%
	p-value	0.44	0.59	0.58	0.18	0.66
Five-yr	Non-TC	84%	95%	89%	47%	89%
	TC	74%	89%	83%	56%	88%
	p-value	0.27	0.2	0.68	0.2	0.67
Ten-yr	Non-TC	63%	86%	81%	47%	49%
	TC	19%	60%	41%	56%	70%
	p-value	0.004	0.04	0.06	0.2	0.65

Table 3. Evaluation of ejection fractions

	TC	Non-TC	p-value
One yr	60.7 ± 7.6%	58.7 ± 7.4%	0.05
Two yr	61.2 ± 5.9%	60.6 ± 7.4%	0.59
Three yr	61.4 ± 5.8%	61.6 ± 4.9%	0.86
Five yr	61.8 ± 6.9%	60.0 ± 8.9%	0.43

Values above are an evaluation of ejection fractions (% ± standard deviation) including values at year one, two, three, and five. TC, tachycardia group; Non-TC, non-tachycardia group.

Table 4. Multivariable Cox regression analysis for all-cause mortality and cardiovascular (CV) mortality

	All-cause mortality		CV mortality	
Variable	HR (95% CI)	p-value	HR (95% CI)	p-value
Recipient age	1.00 (0.96–1.01)	0.24	0.97 (0.93–1.02)	0.19
Donor gender	0.79 (0.38–1.54)	0.45	1.52 (0.48–4.8)	0.47
Donor age	1.01 (0.98–1.05)	0.59	1.04 (0.98–1.09)	0.26
Recipient gender	1.8 (0.77–4.22)	0.17	0.91 (0.24–3.5)	0.89
HF etiology	1.04 (0.51–2.13)	0.92	0.52 (0.12–2.36)	0.40
Recipient BMI	0.98 (0.92–1.05)	0.63	0.8 (0.67–0.96)	0.01
Beta blocker	1.32 (0.66–2.6)	0.43	1.98 (0.59–6.63)	0.27
Heart rate > 100	2.56 (1.19–5.49)	0.02	3.93 (1.17–13.19)	0.03

p-value from multivariable Cox regression models that included all variables shown in the table. Etiology of HF was of the heart transplant recipients and heart rate > 100 were from the 10-yr mortality. HR, hazard ratio; CI, confidence interval, HF, heart hailure, BMI, body mass index.

improve quality of life (19–22). The SHIFT trial studied 6558 patients with heart failure (ejection fraction [EF] <35%) receiving standard medical management (including beta-blockers) and showed that patients randomized to ivabradine had a lower incidence of worsening heart failure and death due to heart failure (15, 23). Importantly, Zhang et al. demonstrated a normalized QT interval and an improved left ventricular mass index with a suggested improvement in cardiopulmonary performance in HT patients taking ivabradine (12). We feel that given the accumulating evidence proposed within this study and elsewhere, a prospective large-scale study evaluating the safety and efficacy of ivabradine in HT patients is warranted.

Conclusion

HT recipients with resting HR greater than 100 bpm appear to have higher all-cause mortality and cardiovascular mortality compared to those with lower resting HR. Whether pharmacological lowering of HR would result in better outcomes, including all-cause mortality and cardiovascular mortality, in this patient population warrants further investigation.

References

1. Levine HJ. Rest heart rate and life expectancy. J Am Coll Cardiol 1997: 30: 1104.
2. Fox K, Ford I, Steg PG, Tendera M, Robertson M, Ferrari R. Heart rate as a prognostic risk factor in patients with coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a subgroup analysis of a randomised controlled trial. Lancet 2008: 372: 817.
3. Fox K, Steg PG. Elevated heart rate proven to increase coronary events. Cardiovasc J Afr 2008: 19: 276.
4. Singh JP, Larson MG, Tsuji H, Evans JC, O'Donnell CJ, Levy D. Reduced heart rate variability and new-onset hypertension: insights into pathogenesis of hypertension: the Framingham Heart Study. Hypertension 1998: 32: 293.

5. Tsuji H, Larson MG, Venditti FJ Jr., et al. Impact of reduced heart rate variability on risk for cardiac events. The Framingham Heart Study. Circulation 1996: 94: 2850.
6. Perret-Guillaume C, Joly L, Benetos A. Heart rate as a risk factor for cardiovascular disease. Prog Cardiovasc Dis 2009: 52: 6.
7. Buendia Fuentes F, Martinez-Dolz L, Almenar Bonet L et al. Normalization of the heart rate response to exercise 6 months after cardiac transplantation. Transplant Proc 2010: 42: 3186.
8. Gilbert EM, Eiswirth CC, Mealey PC, Larrabee P, Herrick CM, Bristow MR. Beta-adrenergic supersensitivity of the transplanted human heart is presynaptic in origin. Circulation 1989: 79: 344.
9. Doesch AO, Ammon K, Konstandin M et al. Heart rate reduction for 12 months with ivabradine reduces left ventricular mass in cardiac allograft recipients. Transplantation 2009: 88: 835.
10. Doesch AO, Celik S, Ehlermann P et al. Heart rate reduction after heart transplantation with beta-blocker versus the selective If channel antagonist ivabradine. Transplantation 2007: 84: 988.
11. Zhang R, Bobylev D, Stiefel P, Haverich A, Bara C. Lasting reduction of heart transplant tachycardia with ivabradine is effective and well tolerated: results of 48-month study. Clin Res Cardiol 2012: 101: 631.
12. Zhang R, Haverich A, Struber M, Simon A, Pichlmaier M, Bara C. Effects of ivabradine on allograft function and exercise performance in heart transplant recipients with permanent sinus tachycardia. Clin Res Cardiol 2008: 97: 811.
13. Arora S, Aukrust P, Andreassen A et al. The prognostic importance of modifiable risk factors after heart transplantation. Am Heart J 2009: 158: 431.
14. Navarro-Manchon J, Martinez-Dolz L, Almenar L et al. Prognostic value of glomerular filtration rate 1 year after heart transplantation. Rev Esp Cardiol 2010: 63: 564.
15. Beck W, Barnard CN, Schrire V. Heart rate after cardiac transplant. Circulation 1969: 40: 437.
16. Arrowood JA, Minisi AJ, Goudreau E, Davis AB, King AL. Absence of parasympathetic control of heart rate after human orthotopic cardiac transplant. Circulation 1997: 96: 3498.
17. Fallen EL, Kamath MV, Ghista DN, Fitchett D. Spectral analysis of heart rate variability following human heart transplant: evidence for functional reinnervation. J Auton Nerv Syst 1988: 23: 199.
18. Bengal FM, Ueberfuhr P, Schiepel N, Nekolla SG, Reichart B, Schwaiger M. Effect of sympathetic reinnervation on cardiac performance after heart transplant. N Engl J Med 2001: 345: 731.
19. Bohm M, Swedberg K, Komajda M et al. Heart rate as a risk factor in chronic heart failure (SHIFT): the association between heart rate and outcomes in a randomised placebo-controlled trial. Lancet 2010: 376: 886.
20. Busseuil D, Shi Y, Mecteau M et al. Heart rate reduction by ivabradine reduces diastolic dysfunction and cardiac fibrosis. Cardiology 2010: 117: 234.
21. Ekman I, Chassany O, Komajda M et al. Heart rate reduction with ivabradine and health related quality of life in patients with chronic heart failure: results from the SHIFT study. Eur Heart J 2011: 32: 2395.
22. Ceconi C, Freedman SB, Tardif JC et al. Effect of heart rate reduction by ivabradine on left ventricular remodeling in the echocardiographic substudy of BEAUTIFUL. Int J Cardiol 2011: 146: 408.
23. Swedberg K, Komajda M, Bohm M et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. Lancet 2010: 376: 875.