Heart and Vessels (2019) 34:318–323
https://doi.org/10.1007/s00380-018-1248-8

ORIGINAL ARTICLE

Preoperative endothelial function and long-term cardiovascular events in patients undergoing cardiovascular surgery

Yuichi Saito[1] · Hideki Kitahara[1] · Goro Matsumiya[2] · Yoshio Kobayashi[1]

Received: 10 June 2018 / Accepted: 17 August 2018 / Published online: 22 August 2018

Abstract

We recently reported that preoperative endothelial dysfunction [i.e., reactive hyperemia index (RHI) ≤ 1.64] predicted short-term postoperative adverse events in patients undergoing cardiovascular surgery. However, the relationship between preoperative RHI and long-term cardiovascular risk in these patients is unclear. A total of 195 patients with at least 1-year follow-up who underwent cardiovascular surgery were included. Preoperative endothelial function was assessed by RHI. The primary outcome was a composite of cardiac death, stroke, myocardial infarction, rehospitalization due to heart failure, and any coronary revascularization. Nineteen patients (9.7%) met the primary outcome, including cardiac death ($n=7$), stroke ($n=5$), heart failure ($n=9$), and coronary revascularization ($n=2$) during a median follow-up of 20 months. There was no significant difference in the baseline characteristics between patients with RHI ≤ 1.64 ($n=86$) and those with RHI > 1.64 ($n=109$). The primary outcome occurred in 13 patients with RHI ≤ 1.64 (15.1%) and in 6 patients with RHI > 1.64 (5.5%). Kaplan–Meier analysis demonstrated a significantly higher incidence of the primary outcome in patients with RHI ≤ 1.64 compared to their counterpart (hazard ratio 2.94; 95% confidence interval 1.12–7.75; $p=0.02$). Multivariate analysis showed diabetes and RHI ≤ 1.64 as independent predictors for the primary outcome. In conclusion, preoperative endothelial dysfunction assessed by RHI was associated with long-term cardiovascular events in patients undergoing cardiovascular surgery.

Keywords Cardiovascular surgery · Endothelial function · Reactive hyperemia index · Outcome

Introduction

Cardiovascular surgery is one of the highest-risk procedures in the field of surgery, despite recent developments in perioperative care and management [1]. Although there are some useful prognostic risk models, such as EuroSCORE II and JapanSCORE [2–4], these scores intrinsically predict short-term perioperative mortality and risks by incorporating several factors, including age, sex, patient complications, and surgical settings [5]. Therefore, the long-term prognostic factors in these patients are still unclear.

The endothelium plays important roles in the regulation of vascular tone, thrombosis, and inflammation [6]. Impairment of endothelial function indirectly assessed by non-invasive tests, such as flow-mediated dilation (FMD) and reactive hyperemia index (RHI), has been reported to lead to increased risk of subsequent cardiovascular events in the general population or in patients with suspected ischemic heart disease [7, 8]. Preoperative endothelial dysfunction has been similarly shown to be a predictor of postoperative adverse events in several types of surgeries [9, 10]. In addition, we have recently reported that preoperative-impaired RHI (i.e., ≤ 1.64) in patients undergoing cardiovascular surgery was associated with short-term postoperative events [11]. However, the data concerning the association during long-term follow-up are lacking. Thus, the aim of this study was to investigate the relation between preoperative RHI as a surrogate marker of endothelial function and long-term adverse events in patients undergoing cardiovascular surgery.

✉ Yuichi Saito
policemaccho@yahoo.co.jp

[1] Department of Cardiovascular Medicine, Chiba University Graduate School of Medicine, 1-8-1 Inohana, Chuo-ku, Chiba, Chiba 260-8677, Japan

[2] Department of Cardiovascular Surgery, Chiba University Graduate School of Medicine, Chiba, Japan

Methods

Study population

From October 2014 to April 2016, a total of 197 patients undergoing elective cardiovascular surgery with thoracotomy and/or laparotomy, such as coronary artery bypass grafting, cardiac valve and aortic surgery under general anesthesia at Chiba University Hospital, were prospectively enrolled, as shown in our previous report, to investigate the association between preoperative endothelial dysfunction and short-term postoperative events [11]. The present study was a post hoc analysis of the previous report. Long-term follow-up (> 1 year) data were obtained via medical records or telephonic interview, and 2 patients were lost to follow-up. Thus, 195 out of 197 patients (99%) were included in the present study. Written informed consent was obtained from all patients, and the ethical committee of Chiba University approved this study.

RH-PAT

Endothelial function was indirectly evaluated by reactive hyperemia-peripheral arterial tonometry (RH-PAT) by EndoPAT2000 device (Itamar Medical, Caesarea, Israel) before cardiovascular surgery during hospitalization. The methodology of RH-PAT measurement has been previously described [9, 11, 12]. Briefly, all patients had fasted and refrained from caffeine, tobacco, and medications for at least 8 h. The test was performed in a quiet and temperature-controlled room in the early morning. A finger probe for RH-PAT was placed on each index finger, and after a baseline period of 5 min, the blood pressure cuff on the test arm was inflated to obtain complete occlusion for 5 min. Thereafter, the cuff was deflated and the hyperemic response of the occluded arm was recorded for another 5 min. The RH-PAT data were automatically analyzed to calculate RHI, which is the ratio of amplitude of the PAT signal after cuff deflation divided by those before cuff inflation, indexed to the contralateral arm.

Endpoints

The primary outcome was a composite of cardiac death, stroke, myocardial infarction, rehospitalization due to heart failure, and any coronary revascularization during the follow-up period [13, 14]. Cardiac death was defined as death due to myocardial infarction, heart failure, or documented sudden death without apparent non-cardiac causes. Stroke was defined as an acute onset of focal or global neurological deficit accompanied by typical findings on brain imaging. Myocardial infarction was defined according to the third universal definition of myocardial infarction > 72 h after cardiovascular surgery [15]. Rehospitalization due to heart failure was defined as readmission with typical clinical findings of heart failure, requiring additional treatment. Any coronary revascularization included all percutaneous coronary interventions and coronary artery bypass grafting after the index cardiovascular surgery. The patients were divided into 2 groups according to the best cut-off value of RHI in our previous report (i.e., 1.64) [11].

Statistical analysis

Statistical analysis was performed with SAS statistical software package version 9.4 (SAS Institute, Cary, NC). Continuous variables are expressed as the mean ± standard deviation. Categorical variables are represented as frequency (%). Continuous variables with normal distribution were compared using Student's *t* test and categorical variables were compared by Fisher's exact test. Kaplan–Meier analysis with the log-rank test was used to compare event-free survival rates in patients with RHI ≤ 1.64 and RHI > 1.64. A Cox proportional-hazards model was used to estimate unadjusted and adjusted hazard ratios with corresponding 95% confidence intervals. The covariates were selected on the basis of an association with the primary outcome in the present study using an inclusion criterion of $p < 0.05$. A value of $p < 0.05$ was considered statistically significant.

Results

As mentioned above, long-term follow-up of at least 1 year was completed in 195 patients. Overall, mean RHI was 1.81 ± 0.48. There was no significant difference in baseline characteristics between patients with RHI ≤ 1.64 ($n = 86$) and those with RHI > 1.64 ($n = 109$) (Table 1). During a median follow-up of 20 months, 19 patients (9.7%) met the primary outcome, including cardiac death ($n = 7$), stroke ($n = 5$), rehospitalization due to heart failure ($n = 9$), and any coronary revascularization ($n = 2$). There was no myocardial infarction during the follow-up period. The primary outcome occurred in 13 patients with RHI ≤ 1.64 (15.1%) and in 6 patients with RHI > 1.64 (5.5%) (Table 2). Kaplan–Meier analysis demonstrated a significantly higher incidence of the primary outcome in patients with RHI ≤ 1.64 compared to their counterpart ($p = 0.02$) (Fig. 1). The results of the univariate and multivariate Cox proportional-hazard regression analyses are shown in Table 3, which indicated diabetes mellitus and RHI ≤ 1.64 as significant and independent predictors for the primary outcome.

Table 1 Patient characteristics

Variable	All ($n=195$)	RHI ≤ 1.64 ($n=86$)	RHI > 1.64 ($n=109$)	p value
Age (years)	70.1 ± 10.8	70.0 ± 10.3	70.2 ± 11.1	0.92
Men	128 (66%)	56 (65%)	72 (66%)	1.00
Body mass index (kg/m^2)	23.1 ± 3.3	23.2 ± 3.2	23.0 ± 3.4	0.68
Hypertension	138 (71%)	64 (74%)	74 (68%)	0.34
Diabetes mellitus	45 (23%)	17 (20%)	28 (26%)	0.39
Dyslipidemia	129 (66%)	61 (71%)	68 (62%)	0.23
Current smoker	29 (15%)	14 (16%)	15 (14%)	0.69
eGFR (ml/min/1.73 m^2)	55.8 ± 19.2	54.7 ± 17.5	56.7 ± 20.5	0.47
Left-ventricular ejection fraction (%)	58.7 ± 11.2	57.1 ± 12.6	60.0 ± 9.8	0.07
Medication				
ACE-I or ARB	107 (55%)	51 (59%)	56 (51%)	0.31
β-blocker	62 (32%)	26 (30%)	36 (33%)	0.76
Diuretic	72 (37%)	38 (44%)	34 (31%)	0.07
Statin	89 (46%)	43 (50%)	46 (42%)	0.31
Type of surgery				
CABG	70 (36%)	30 (35%)	40 (37%)	0.88
Aortic valve surgery	71 (36%)	33 (38%)	38 (35%)	0.65
Mitral valve surgery	56 (29%)	30 (35%)	26 (24%)	0.11
Tricuspid valve surgery	31 (16%)	16 (19%)	15 (14%)	0.43
Thoracic aortic surgery	33 (17%)	16 (19%)	17 (16%)	0.70
Abdominal aortic surgery	10 (5%)	5 (6%)	5 (5%)	0.75
LAA closure and/or maze procedure	27 (14%)	15 (17%)	12 (11%)	0.22
Other	16 (8%)	8 (9%)	8 (7%)	0.79
Reactive hyperemia index	1.81 ± 0.48	1.42 ± 0.15	2.11 ± 0.44	< 0.001

ACE-I angiotensin converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *CABG* coronary artery bypass grafting, *eGFR* estimated glomerular filtration rate, *LAA* left atrial appendage, *RHI* reactive hyperemia index

Table 2 Primary endpoint

Variable	All ($n=195$)	RHI ≤ 1.64 ($n=86$)	RHI > 1.64 ($n=109$)	p value
Primary endpoint	19 (9.7%)	13 (15.1%)	6 (5.5%)	0.03
Cardiac death	7 (3.6%)	6 (7.0%)	1 (0.9%)	0.045
Stroke	5 (2.6%)	4 (4.7%)	1 (0.9%)	0.17
Myocardial infarction	0 (0%)	0 (0%)	0 (0%)	–
Rehospitalization due to HF	9 (4.6%)	6 (7.0%)	3 (2.8%)	0.19
Any coronary revascularization	2 (1.0%)	1 (1.2%)	1 (0.9%)	1.00

HF heart failure, *RHI* reactive hyperemia index

Discussion

The present study demonstrated that preoperative RHI had a predictive value for long-term cardiovascular events in patients undergoing cardiovascular surgery, as well as diabetes mellitus.

Role of endothelial function

Since the endothelial cells regulate vascular tone, thrombosis, and inflammation [6], endothelial dysfunction is reportedly related to cardiovascular events [7, 8]. It is conceivable that endothelial dysfunction induces atherosclerotic

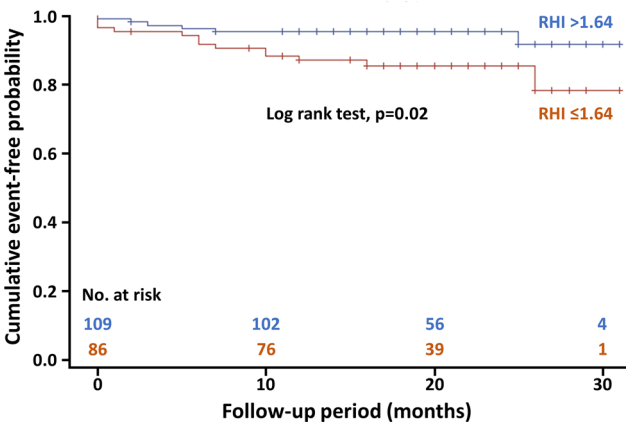

Fig. 1 Kaplan–Meier analysis for the probability of the primary outcome consists of cardiac death, stroke, myocardial infarction, rehospitalization due to heart failure, and any coronary revascularization in patients with RHI ≤ 1.64 and those with RHI > 1.64. *RHI* reactive hyperemia index

progression and thrombus formation, and future adverse events, such as myocardial infarction and stroke [16, 17]. Patients with endothelial dysfunction also have limited arterial vasodilatory response, which may impair cardiac output reserve [18], leading consequently, to heart failure. In addition, inflammation is associated with a wide range of cardiovascular outcomes [19].

Endothelial dysfunction and long-term cardiovascular events

RHI can non-invasively and operator-independently assess endothelial function with excellent reproducibility [20–22], however, it is an indirect surrogate marker [23]. RHI < 1.67 has been conventionally indicated as endothelial dysfunction [14], which is very similar to our previous result of the best cut-off value for predicting short-term postoperative adverse events (i.e., 1.64) [11]. Although, with that threshold, impaired endothelial function was associated with postoperative events, the long-term prognostic impact of endothelial dysfunction assessed by RHI in patients undergoing cardiovascular surgery was unknown. Thus, the present study first reported preoperative RHI as a long-term prognostic factor in patients with cardiovascular surgery. Recent meta-analysis revealed that RHI had a long-term prognostic value in patients with suspected ischemic heart disease, established coronary artery disease, and heart failure with preserved ejection fraction [24]. One of the studies with the longest follow-up period (i.e., 7 years) reported that the patients with low RHI had a significantly higher incidence of cardiovascular death and hospitalization due to cardiovascular causes, and numerically greater number of strokes compared to those with high RHI [8]. Another study investigating subjects with heart failure also indicated that the patients with low RHI had a numerically higher incidence of cardiovascular death and significantly more hospitalizations due to heart failure than their counterparts [14]. These results are consistent with the present study. On the other hand, there were no myocardial infarctions and only 2 revascularizations in the present study. Thus, the relation between endothelial function and coronary events was not elucidated in this particular population, possibly due to the small number of the events. Although there was a relatively large study reporting that patients with low RHI underwent more subsequent coronary revascularization [13], the recent annual rate of myocardial infarction beyond the acute phase of cardiovascular surgery is < 1%, even in patients with coronary bypass grafting involving the left main trunk [25]. As a result, this study indicated that the patients with impaired RHI were likely to develop future cardiovascular events, predominantly comprised of cardiac death, stroke, and rehospitalization due to heart failure in patients undergoing cardiovascular surgery.

Potential implication to evaluate preoperative endothelial function

In addition to risk stratification, the potential importance of evaluating endothelial function is underscored by previous studies which showed that patients without improvement in endothelial function are associated with cardiovascular events [26]. Endothelial function can be improved by some interventions such as diet, exercise and medications, including renin–angiotensin system inhibitors or statins [27–29]. Patients undergoing cardiac surgery are still challenging, with a high incidence of subsequent cardiovascular events

Table 3 Cox proportional-hazards analysis for cardiovascular events

Variable	Univariable		Multivariable	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Diabetes mellitus	4.22 (1.70–10.46)	0.002	3.57 (1.34–9.36)	0.01
eGFR (ml/min/1.73 m^2)	0.97 (0.95–0.998)	0.04		
Left-ventricular ejection fraction (%)	0.96 (0.93–0.99)	0.02		
Reactive hyperemia index ≤ 1.64	2.94 (1.11–7.75)	0.03	2.79 (1.03–7.53)	0.04

CI confidence intervals, *eGFR*, estimated glomerular filtration rate, *HR* hazard ratio

[30]. Therefore, implementing a perioperative strategy to improve endothelial function may ameliorate long-term outcomes in patients undergoing cardiovascular surgery.

Study limitations

There are several limitations in this study. First, this is a post hoc analysis of a single center study, and the number of included patients was relatively small. However, all patients were prospectively enrolled and the follow-up rate was high (99%). Second, the patients with not only cardiac surgery, but also thoracic and abdominal aortic surgery were included into this study. Third, endothelial function was evaluated by RHI in the present study, while FMD has been used in a number of previous studies. RHI has no apparent correlation with FMD [31], and additionally both RHI and FMD are indirect assessments of endothelial function. Thus, using RHI and FMD as surrogate markers of endothelial function remains controversial [23]. Although endothelium-independent nitroglycerin-mediated vasodilation should be compared with endothelium-dependent reactive hyperemia to purely test it, endothelium-independent vasodilating examinations were not conducted in the present study. RHI and FMD can indirectly assess endothelial function from different aspects, and are reported to predict cardiovascular events with a similar prognostic magnitude [24]. Fourth, RHI was measured once before cardiovascular surgery in the present study. However, the test–retest reliability of RHI has been reported to be acceptable [22].

Conclusion

Preoperative endothelial dysfunction assessed by RHI was associated with long-term cardiovascular events in patients undergoing cardiovascular surgery.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Motomura N, Miyata H, Tsukihara H, Takamoto S (2008) Risk model of thoracic aortic surgery in 4707 cases from a nationwide single-race population through a web-based data entry system: the first report of 30-day and 30-day operative outcome risk models for thoracic aortic surgery. Circulation 118:S153–S159
2. Nashef SA, Roques F, Sharples LD, Nilsson J, Smith C, Goldstone AR, Lockowandt U (2012) EuroSCORE II. Eur J Cardiothorac Surg 41:734–744
3. Miyata H, Motomura N, Tsukihara H, Takamoto S (2011) Risk models including high-risk cardiovascular procedures: clinical predictors of mortality and morbidity. Eur J Cardiothorac Surg 39:667–674
4. Saito A, Motomura N, Miyata H, Takamoto S, Kyo S, Ono M (2011) Age-specific risk stratification in 13488 isolated coronary artery bypass grafting procedures. Interact Cardiovasc Thorac Surg 12:575–580
5. Hansen LS, Sloth E, Hjortdal VE, Jakobsen CJ (2015) Follow-up after cardiac surgery should be extended to at least 120 days when benchmarking cardiac surgery centers. J Cardiothorac Vasc Anesth 29:984–989
6. Gokce N, Keaney JF Jr, Hunter LM, Watkins MT, Nedeljkovic ZS, Menzoian JO, Vita JA (2003) Predictive value of noninvasively determined endothelial dysfunction for long-term cardiovascular events in patients with peripheral vascular disease. J Am Coll Cardiol 41:1769–1775
7. Yeboah J, Crouse JR, Hsu FC, Burke GL, Herrington DM (2007) Brachial flow-mediated dilation predicts incident cardiovascular events in older adults: the cardiovascular health study. Circulation 115:2390–2397
8. Rubinshtein R, Kuvin JT, Soffler M, Lennon RJ, Lavi S, Nelson RE, Pumper GM, Lerman LO, Lerman A (2010) Assessment of endothelial function by non-invasive peripheral arterial tonometry predicts late cardiovascular adverse events. Eur Heart J 31:1142–1148
9. Suzuki H, Matsuzawa Y, Konishi M, Akiyama E, Takano K, Nakayama N, Kataoka S, Ebina T, Kosuge M, Hibi K, Tsukahara K, Iwahashi N, Endo M, Maejima N, Shinohara K, Taki N, Mitsugi N, Taguri M, Sugiyama S, Ogawa H, Umemura S, Kimura K (2014) Utility of noninvasive endothelial function test for prediction of deep vein thrombosis after total hip or knee arthroplasty. Circ J 78:1723–1732
10. Schier R, Hinkelbein J, Marcus H, Mehran R, El-Zein R, Hofstetter W, Swafford J, Riedel B (2012) Preoperative microvascular dysfunction: a prospective, observational study expanding risk assessment strategies in major thoracic surgery. Ann Thorac Surg 94:226–233
11. Saito Y, Kitahara H, Matsumiya G, Kobayashi Y (2017) Preoperative assessment of endothelial function for prediction of adverse events after cardiovascular surgery. Circ J 82:118–122
12. Kuvin JT, Patel AR, Sliney KA, Pandian NG, Sheffy J, Schnall RP, Karas RH, Udelson JE (2003) Assessment of peripheral vascular endothelial function with finger arterial pulse wave amplitude. Am Heart J 146:168–174
13. Matsuzawa Y, Sugiyama S, Sumida H, Sugamura K, Nozaki T, Ohba K, Matsubara J, Kurokawa H, Fujisue K, Konishi M, Akiyama E, Suzuki H, Nagayoshi Y, Yamamuro M, Sakamoto K, Iwashita S, Jinnouchi H, Taguri M, Morita S, Matsui K, Kimura K, Umemura S, Ogawa H (2013) Peripheral endothelial function and cardiovascular events in high-risk patients. J Am Heart Assoc 2:e000426
14. Akiyama E, Sugiyama S, Matsuzawa Y, Konishi M, Suzuki H, Nozaki T, Ohba K, Matsubara J, Maeda H, Horibata Y, Sakamoto K, Sugamura K, Yamamuro M, Sumida H, Kaikita K, Iwashita S, Matsui K, Kimura K, Umemura S, Ogawa H (2012) Incremental prognostic significance of peripheral endothelial dysfunction in patients with heart failure with normal left ventricular ejection fraction. J Am Coll Cardiol 60:1778–1786
15. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD (2012) Third universal definition of myocardial infarction. Circulation 126:2020–2035
16. Widlansky ME, Gokce N, Keaney JF Jr, Vita JA (2003) The clinical implications of endothelial dysfunction. J Am Coll Cardiol 42:1149–1160
17. Yau JW, Teoh H, Verma S (2015) Endothelial cell control of thrombosis. BMC Cardiovasc Disord 15:130

18. Borlaug BA, Melenovsky V, Russell SD, Kessler K, Pacak K, Becker LC, Kass DA (2006) Impaired chronotropic and vasodilator reserves limit exercise capacity in patients with heart failure and a preserved ejection fraction. Circulation 114:2138–2147
19. Huynh K (2017) Inflammation: Targeting inflammatory pathways to treat atherosclerosis and cancer. Nat Rev Cardiol 14:629
20. Selamet Tierney ES, Newburger JW, Gauvreau K, Geva J, Coogan E, Colan SD, de Ferranti SD (2009) Endothelial pulse amplitude testing: feasibility and reproducibility in adolescents. J Pediatr 154:901–905
21. Bonetti PO, Pumper GM, Higano ST, Holmes DR Jr, Kuvin JT, Lerman A (2004) Noninvasive identification of patients with early coronary atherosclerosis by assessment of digital reactive hyperemia. J Am Coll Cardiol 44:2137–2141
22. Sauder KA, West SG, McCrea CE, Campbell JM, Jenkins AL, Jenkins DJ, Kendall CW (2014) Test–retest reliability of peripheral arterial tonometry in the metabolic syndrome. Diab Vasc Dis Res 11:201–207
23. Gokce N (2011) Clinical assessment of endothelial function: ready for prime time? Circ Cardiovasc Imaging 4:348–350
24. Matsuzawa Y, Kwon TG, Lennon RJ, Lerman LO, Lerman A (2015) Prognostic value of flow-mediated vasodilation in brachial artery and fingertip artery for cardiovascular events: a systematic review and meta-analysis. J Am Heart Assoc 4:e002270
25. Stone GW, Sabik JF, Serruys PW, Simonton CA, Généreux P, Puskas J, Kandzari DE, Morice MC, Lembo N, Brown WM 3rd, Taggart DP, Banning A, Merkely B, Horkay F, Boonstra PW, van Boven AJ, Ungi I, Bogáts G, Mansour S, Noiseux N, Sabaté M, Pomar J, Hickey M, Gershlick A, Buszman P, Bochenek A, Schampaert E, Pagé P, Dressler O, Kosmidou I, Mehran R, Pocock SJ, Kappetein AP, Trial Investigators EXCEL (2016) Everolimus-eluting stents or bypass surgery for left main coronary artery disease. N Engl J Med 375:2223–2225
26. Kitta Y, Obata JE, Nakamura T, Hirano M, Kodama Y, Fujioka D, Saito Y, Kawabata K, Sano K, Kobayashi T, Yano T, Nakamura K, Kugiyama K (2009) Persistent impairment of endothelial vasomotor function has a negative impact on outcome in patients with coronary artery disease. J Am Coll Cardiol 53:323–330
27. Matsuzawa Y, Sugiyama S, Sugamura K, Sumida H, Kurokawa H, Fujisue K, Konishi M, Akiyama E, Suzuki H, Nakayama N, Yamamuro M, Iwashita S, Jinnouchi H, Kimura K, Umemura S, Ogawa H (2013) Successful diet and exercise therapy as evaluated on self-assessment score significantly improves endothelial function in metabolic syndrome patients. Circ J 77:2807–2815
28. Shahin Y, Khan JA, Samuel N, Chetter I (2011) Angiotensin converting enzyme inhibitors effect on endothelial dysfunction: a meta-analysis of randomised controlled trials. Atherosclerosis 216:7–16
29. Dupuis J, Tardif JC, Cernacek P, Théroux P (1999) Cholesterol reduction rapidly improves endothelial function after acute coronary syndromes. The RECIFE (reduction of cholesterol in ischemia and function of the endothelium) trial. Circulation 99:3227–3233
30. Parikh CR, Puthumana J, Shlipak MG, Koyner JL, Thiessen-Philbrook H, McArthur E, Kerr K, Kavsak P, Whitlock RP, Garg AX, Coca SG (2017) Relationship of kidney injury biomarkers with long-term cardiovascular outcomes after cardiac surgery. J Am Soc Nephrol 28:3699–3707
31. Hamburg NM, Palmisano J, Larson MG, Sullivan LM, Lehman BT, Vasan RS, Levy D, Mitchell GF, Vita JA, Benjamin EJ (2011) Relation of brachial and digital measures of vascular function in the community: the Framingham heart study. Hypertension 57:390–396