Impact of energy loss index on left ventricular mass regression after aortic valve replacement

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Title:

Impact of Energy Loss Index on Left Ventricular Mass Regression after Aortic Valve Replacement

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Abstract

Background: Recently, energy loss index (ELI) has been proposed as a new functional index to assess severity of aortic stenosis (AS). The aim of this study was to investigate the impact of ELI on ventricular mass (LVM) regression in patients after aortic valve replacement (AVR) with mechanical valves.

Methods: A total of 30 patients with severe AS who underwent AVR with mechanical valves was studied. Echocardiography was performed to measure LVM before AVR (pre-LVM) (n=30) and repeated 12 months later (post-LVM) (n=19). ELI was calculated as [effective orifice area (EOA) x aortic cross sectional area] / (aortic cross sectional area – EOA) divided by body surface area (BSA). LVM regression rate (%) was calculated as 100 x (Post-LVM – Pre-LVM) / (Pre-LVM). Cardiac event was defined as a composite of cardiac death and heart failure requiring hospitalization.

Results: LVM regressed significantly (245.1±84.3 to 173.4±62.6g, P<0.01) at 12 months after AVR. LVM regression rate negatively correlated with ELI (r=-0.67, P<0.01). By receiver operating characteristics analysis, ELI < 1.12 cm²/m² predicted smaller (< -30.0 %) LVM regression rate (area under curve =0.825; p=0.030). Patients with ELI < 1.12 cm²/m² had significantly lower cardiac event-free survival.

Conclusion: ELI as well as EOAI could predict LVM regression after AVR with mechanical valves. Whether ELI is stronger predictor of clinical events than EOAI is still unclear, further large scale study is necessary to elucidate clinical impact of ELI in patients with AVR.
Keywords:

prosthesis-patient mismatch

aortic valve replacement

aortic stenosis

energy loss coefficient

energy loss index
Introduction

Prosthesis–patient mismatch (PPM) was first described as a condition where the effective orifice area (EOA) of normally functioning heart valve prosthesis is too small in relation to the patient's body size, which results in high transvalvular pressure gradients [1]. Patients with PPM have worse functional class and exercise capacity, reduced regression of left ventricular (LV) hypertrophy after aortic valve replacement (AVR) compared with patients without PPM [2, 3]. Furthermore, PPM has been associated with increased incidence of late cardiac events [4-8].

Although EOA derived from continuity equation or direct planimetry of the stenotic aortic valve orifice were used to assess severity of the aortic stenosis (AS) [9, 10], overestimation of EOA could occur in the clinical setting because of the pressure recovery phenomenon [11, 12]. Doppler-derived energy loss coefficient (ELCo) or energy loss index (ELI) has been proposed as a functional index to assess severity of AS [11-13]. Although ELCo or ELI may be related to LV mass (LVM) regression after AVR with bioprosthetic valves [14], impact of ELI on LVM regression and clinical event after AVR with mechanical valves in patients with AS is unknown. Therefore, the objective of this study was to investigate the impact of ELI on LVM regression in patients who underwent AVR with mechanical valves.
Methods

Patients

This study population included consecutive 30 patients (62.8 ± 7.7 years; 15 men) with severe aortic stenosis who underwent AVR with mechanical valves at our center between March 2002 and December 2010.

Indications for AVR were symptomatic severe AS (n = 20), asymptomatic severe AS with a high likelihood of rapid progression (n = 4), asymptomatic severe AS undergoing CABG (n = 3), and extremely severe AS (peak aortic jet velocity > 5.0 m/second, n = 3).

The prosthetic valves used in this study were the ATS (ATS Medical, Inc., Minneapolis, MN, USA) in 13 patients (valve size 19 mm, n = 4; valve size 21 mm, n = 2; valve size 23 mm, n = 6; valve size 25 mm, n = 1), the ATS AP (ATS Medical, Inc., Minneapolis, MN, USA) in 3 patients (valve size 18 mm, n = 2; valve size 24 mm, n = 1), the St. Jude Medical Standard (Medtronic, Minneapolis, MN, USA) in 3 patients (valve size 19 mm, n = 2; valve size 21 mm, n = 1), the St. Jude Medical Regent in 3 patients (valve size 19 mm, n = 2; valve size 23 mm, n = 1), the MCRI On-X valve (Medical Carbon Research Institute, LLC, Austin, Tex) in 3 patients (valve size 19 mm, n = 2; valve size 21 mm, n = 1), the Edwards Mira (Edwards Lifesciences, Irvine, CA, USA) in 1 patient (valve size 19 mm), and the Carbomedics Standard (Sulzer Carbomedics, Austin, TX, USA) in 4 patients (valve size 19 mm, n = 2; valve size 21 mm, n = 2). The study protocol was approved by the ethics committee of Kawasaki Medical
School, and informed consent was given by each patient.

Presence of hypertension, hyperlipidemia, or diabetes mellitus was determined using the following criteria. Hypertension was defined as blood pressure > 140 / 90 mmHg or current use of antihypertensive medication. Hyperlipidemia was defined as total cholesterol level > 220 mg / dL or triglyceride level > 150 mg / dL or current use of lipid lowering medication. Diabetes mellitus was defined as fasting plasma glucose level > 126 mg / dL, plasma glucose level (at any time) > 200 mg / dL, or current use of anti-diabetic medication. We excluded patients with systolic LV dysfunction before or after AVR (LV ejection fraction < 30%).

**Echocardiography**

Echocardiographic examinations were performed before, 1 month and 12 months after AVR. Echocardiographic parameters included LV dimension, LV wall thickness, LV ejection fraction, and LVM. LV dimension and LV wall thickness were measured using the 2-dimensional method, and LV ejection fraction was measured using the modified Simpson’s method [15]. LVM was calculated using the method of Devereux et al [16]. Changes in LVM were assessed using both absolute LVM regression and LVM regression rate. Absolute LVM regression (grams) was calculated as post-LVM – pre-LVM. LVM regression rate (%) was calculated as 100 x (post-LVM - pre-LVM) / pre-LVM [4]. The transvalvular gradients were measured using a continuous-wave Doppler technique. Pre-operative EOA was calculated according to the continuity equation. EOA index (EOAI) was calculated as EOA divided
by BSA. Aortic diameter was measured at the level of the sinotubular junction \[17\]. Aortic cross-sectional area (AA) was calculated as $3.14 \times \left(\frac{\text{aortic diameter}}{2}\right)^2$. ELCo was calculated as $\frac{\text{EOA} - \text{AA}}{\text{AA} - \text{EOA}}$ \[12, 13, 18\]. ELI was calculated as ELCo divided by BSA. Known EOA value for each prosthetic valve was used to calculate ELCo \[4, 12, 19-21\]. The change in EOAI (ΔEOAI) (cm\(^2\)/m\(^2\)) after AVR was calculated as Post-operative EOAI - Pre-operative EOAI. The change in ELI (ΔELI) (cm\(^2\)/m\(^2\)) was calculated as Post-operative ELI - Pre-operative ELI \[22\].

Cardiac event was defined as a composite of cardiac death and heart failure requiring hospitalization.

**Statistical Methods**

All data were statistically analyzed using the SPSS statistical software (version 20.0, SPSS Inc, Chicago, IL). The continuous variables were expressed as mean ± standard deviation and compared using a two-tailed paired Student's t test. Comparison between the two main groups was made with Fisher’s exact tests for categorical variables. For continuous variables, ANOVA with post-hoc analysis using the Scheffe test was used to differentiate among 3 groups of data. The relationship between LVM regression rate and the EOAI or the ELI was evaluated by means of simple linear regression analysis to calculate $r$ (Pearson's correlation coefficient). Using receiver-operating characteristic (ROC) curves (ie, plots of sensitivity vs 1 minus specificity), we defined the best cutoff value of ELI for detecting patients with higher LVM regression rate after AVR and survival and freedom from cardiac events. A p value of less than 0.05 was considered significant.
Results

The baseline clinical characteristics are summarized in Table 1. Twenty six of 30 patents had symptoms related to severe AS. Echocardiographic findings before, 1 month and 12 months after AVR were shown on Table 2. Eleven of 30 patients have no echocardiographic data at 12 months because they were followed at other hospitals without routine echocardiographic examinations. LV diastolic diameter, interventricular septal thickness, posterior wall thickness and LVM significantly decreased. The mean values of absolute LVM regression and LVM regression rate from before AVR to 12 months after AVR were -76.8 ± 37.9 g and -30.0 ± 9.26 %, respectively. After AVR, peak aortic velocity and mean pressure gradient decreased significantly (Table 3).

There were no significant correlations between peak aortic velocity after AVR and absolute LVM regression (R = -0.411, P = 0.080) or LVM regression rate (R = -0.222, P = 0.360). On the other hand, negative correlations were observed between post-operative EOAI and LVM absolute regression (R = -0.543, P = 0.016) or LVM regression rate (R = -0.658, P = 0.002) (Fig. 1). Similarly, post-operative ELI correlated negatively with absolute LVM regression (R = -0.511, P = 0.026) or LVM regression rate (R = -0.670, P = 0.002) (Fig. 2). LVM regression rate correlated negatively with both ΔEOAI (R = -0.601, P = 0.007) and ΔELI (R = -0.655, P = 0.002) (Fig. 3). Similarly, LVM regression rate from 1 month to 12 months after AVR correlated negatively with both ΔEOAI (R = -0.555, P = 0.026) and ΔELI (R = -0.574, P = 0.020) (Fig. 4). The mean value of LVM regression rate was 30.0%. Clinical characteristics and...
echocardiographic indices were compared between patients with smaller (< -30.0 %) and larger (≥ -30.0 %) LVM regression rate (Table 4 and 5). There were no significant differences in clinical characteristics between patients with smaller and larger LVM regression rate. Similarly, Pre-AVR echocardiographic indices did not differ between the 2 groups. On the other hand, larger LVM regression group had significantly lower peak aortic velocity and mean pressure gradient, and significantly larger ELI after AVR. By ROC analysis, post-operative EOAI < 0.91 cm² / m² or post-operative ELI < 1.12 cm² / m² predicted smaller LVM regression rate (EOAI: area under curve = 0.799; p = 0.011 and ELI: area under curve = 0.799; p = 0.011, respectively).

During follow-up period (median 5.2 years), patients with post-operative EOAI < 0.91 cm² / m² or post-operative ELI < 1.12 cm² / m² had significantly higher incidence of cardiac events (2 cardiac death and 1 heart failure) than patients with post-operative EOAI ≥ 0.91 cm² / m² or post-operative ELI < 1.12 cm² / m². By Kaplan-Meier analysis, cardiac event-free survival was significantly lower in patients with post-operative EOAI < 0.91 cm² / m² or post-operative ELI < 1.12 cm² / m² than in patients with post-operative EOAI ≥ 0.91 cm² / m² or post-operative ELI < 1.12 cm² / m² (Fig. 5 and 6).

Discussion

Main findings of this study were that (1) LVM regression rate negatively and significantly correlated with ELI, (2) ELI < 1.12 cm² / m² predicted smaller LVM regression rate (< -30.0 %) after AVR, and (3) Patients with ELI < 1.12 cm² / m² had higher incidence of cardiac events after AVR.
In our daily clinical settings, peak transaortic flow velocity, mean pressure gradient, as well as EOA derived from continuity equation method are used to assess severity of AS [23]. However, these measurements could be overestimated because of the pressure recovery phenomenon [11-13]. The concept of the pressure recovery phenomenon is based on fluid mechanics theory showing that static pressure downstream of the stenosis could be increased or recovered because of reconversion of kinetic energy into potential energy. Therefore, peak or mean pressure gradient calculated from maximal Doppler flow velocity could overestimate the true pressure gradient through the stenotic orifice. Recently, ELCo or ELI has been proposed as a new Doppler derived index to represent functional severity of AS similar to catheter derived aortic valve area [11, 13, 18]. Previous studies have shown that EOA in patients with AS can be corrected as ELCo using the size of ascending aorta [12, 13]. Several studies have documented that Doppler derived ELCo (or ELI) correlated better with catheter derived aortic valve area than EOA (or EOAI) [11-13]. Interestingly, previous studies demonstrated that substantial numbers of patients who were initially diagnosed as severe AS based on EOA may be re-categorized as moderate AS based on ELCo [11, 24].

Pressure recovery may affect assessment of transprosthetic valvular pressure gradient resulting in overestimation of the severity of prosthetic valvular stenosis [25, 26]. Aljassim et al reported that even in patients with aortic prosthetic valves, the overestimation of the Doppler derived indices can be predicted and corrected using the validated equation to calculate ELCo in AS [27]. Furthermore, our
preliminary observation has shown that ELCo predicts LVM regression in patients after AVR using bioptosthetic valves [14]. Because mechanical prosthetic valves have more complex orifice geometry as compared with bioptosthetic valves, it has not been well investigated if ELCo / ELI predicts LVM regression as well as prognosis. To the best of our knowledge, this is the first report to elucidate the significant relationship between ELI and LVM regression after AVR with mechanical valves. In combination with previous reports and our present results, ELI could be used as a functional index to assess LV pressure overload even after AVR and possibly used as an index for predicting LVM regression after AVR with prosthetic valves [5, 11]. Although LVM could be related to the severity of AS before AVR, indices of AS severity did not predict LVM regression after AVR, probably because AVR itself dramatically change the severity of AS and thus pressure overload to the LV.

PPM is present when the inserted prosthetic valve is too small relative to the patient’s body size. PPM, defined as an EOAI ≤ 0.8 to 0.9 cm$^2$/m$^2$, has been shown to predict adverse outcomes [3-5, 7, 8, 14, 19, 22]. A recent meta-analysis of 34 observational studies including 27,186 patients showed a significant reduction in overall and cardiac-related long-term survival for patients with PPM after AVR [28]. Theoretically, ELI reflects LV pressure overload better than EOAI.

In this study, 9 patients were diagnosed as classical PPM (defined as EOAI< 0.85 cm$^2$/m$^2$). In 7 of 9 patients with EOAI < 0.85 cm$^2$/m$^2$, ELI was ≥ 0.85 cm$^2$/m$^2$. LV mass regression after AVR was numerically greater in patients with ELI ≥ 0.85 cm$^2$/m$^2$ than in patients with ELI < 0.85 cm$^2$/m$^2$. 
(-30.9 ± 9.2% vs -22.2 ± 7.4%), although the difference could not be statistically tested because of small sample size. However, impact of ELI on clinical event after AVR with mechanical valves has not been clarified yet. Although ELI < 1.12 cm²/m² had more cardiac events after AVR in our present study, it is still inconclusive whether ELI is stronger predictor of cardiac events than EOAI because of small sample size and relatively lower events rates in our current study population.

Limitations

The main limitation of this study is that this is a retrospective, single center study with small sample size. As mentioned in the discussion, impact of ELI on clinical outcome might be affected by possible selection bias. In fact, 37% of our current study population was chronic renal failure patients on hemodialysis, who were known to have a very high risk for operative and late mortality [29]. Therefore, this study may be underpowered to be generalized to all the AS patients.

Another limitation of this study is possible changes in aortic diameter after AVR. Botzenhardt et al reported that aortic diameters decreased after removal of the diseased valve [30]. Therefore, changes in aortic diameter after AVR might have affected the results. Different kind of mechanical prosthetic valves have their own flow property although all valves analyzed in this study were bi-leaflet mechanical valves. Therefore, these differences in prosthetic valve type might have affected the results of our present study.

Conclusions

ELI as well as EOAI could predict LVM regression after AVR with mechanical valves. Whether ELI is
stronger predictor of clinical events than EOAI is still unclear, further large scale study is necessary to elucidate clinical impact of ELI in patients with AVR.
Conflict of Interest

Terumasa Koyama, Hiroyuki Okura, Teruyoshi Kume, Kenzo Fukuhara, Koichiro Imai, Akihiro Hayashida, Yoji Neishi, Takahiro Kawamoto, Kazuo Tanemoto and Kiyoshi Yoshida. declare that they have no conflict of interest.

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Figure Legends

**Fig. 1** Comparison between effective orifice area index (EOAI) after AVR and absolute LVM regression (A) and LVM regression rate (B). Both absolute LVM regression and LVM regression rate correlated negatively with EOAI.
**Fig. 2** Comparison between energy loss index (ELI) after AVR and absolute LVM regression (A) and LVM regression rate (B). Both absolute LVM regression and LVM regression rate correlated negatively with ELI.
Fig. 3  Comparison between LVM regression rate and the increases in effective orifice area index (ΔEOAI) or energy loss index (ΔELI) after AVR. Negative correlations were observed between LVM regression rate and ΔEOAI (R = -0.601, P = 0.007) or ΔELI (R = -0.655, P = 0.002) after AVR.
Fig. 4  Comparison between LVM regression rate from 1 month to 12 months after AVR and the increases in effective orifice area index (ΔEOAI) or energy loss index (ΔELI) after AVR. Negative correlations were observed between LVM regression rate and ΔEOAI (R = -0.555, P = 0.026) or ΔELI (R = -0.574, P = 0.020) after AVR.
Fig. 5  Kaplan-Meier curves comparing patients with effective orifice area index (EOAI) $\geq 0.91 \, \text{cm}^2 / \text{m}^2$ versus EOAI $< 0.91 \, \text{cm}^2 / \text{m}^2$. Event-free survival was significantly lower in patients with EOAI $< 0.91 \, \text{cm}^2 / \text{m}^2$. 
Fig. 6 Kaplan-Meier curves comparing patients with energy loss index (ELI) $\geq 1.12$ cm$^2$ / m$^2$ versus ELI $< 1.12$ cm$^2$ / m$^2$. Event-free survival was significantly lower in patients with ELI $< 1.12$ cm$^2$ / m$^2$. 