

Associations of increased arterial stiffness with left ventricular ejection performance and right ventricular systolic pressure in mitral regurgitation before and after surgery: Wave intensity analysis



Kiyomi Niki^{a,*}, Motoaki Sugawara^b, Hiroshi Kayanuma^c, Itaru Takamisawa^d, Hiroyuki Watanabe^e, Keitaro Mahara^d, Tetsuya Sumiyoshi^d, Takao Ida^f, Shuichiro Takanashi^f, Hitonobu Tomoike^d

^a Department of Medical Engineering, Tokyo City University, 1-28-1 Tamazutsumi, Setagaya, Tokyo, Japan

^b Department of Medical Engineering, Himeji Dokkyo University, 7-2-1 Kamiohno, Himeji, Japan

^c Graduate School of Engineering, Tokyo City University, 1-28-1 Tamazutsumi, Setagaya, Tokyo, Japan

^d Department of Cardiology, Sakakibara Heart Institute, 3-16-1 Asahicho, Fuchu, Tokyo, Japan

^e Department of Cardiology, Tokyo Bay Urayasu Ichikawa Medical Center, 3-4-32 Todajima, Urayasu, Chiba, Japan

^f Department of Cardiovascular Surgery, Sakakibara Heart Institute, 3-16-1 Asahicho, Fuchu, Tokyo, Japan

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ABSTRACT

Background: The effect of increased arterial stiffness on mitral regurgitation (MR) is not clear. Using wave intensity (WI) analysis, which is useful for analyzing ventriculo-arterial interaction, we aimed to elucidate associations of increased arterial stiffness with left ventricular (LV) ejection performance and right ventricular systolic pressure (RVSP) in MR.

Methods and Results: We noninvasively measured carotid arterial WI and stiffness parameter (β) in 98 patients with non-ischemic chronic MR before and after surgery, and 98 age-and-gender matched healthy subjects by ultrasonography. WI is defined as $WI = (dP/dt)(dU/dt)$ [P: blood pressure, U: velocity, t: time]. The peak value of WI (W_1) increases with LV peak dP/dt . The temporal WI index ($Q-W_1$)_{st}, which is the standardized interval between the Q wave of the ECG and W_1 , is a surrogate for preejection period. Ejection fraction (EF), left atrial volume index (LAVI), effective regurgitant orifice area (ERO), RVSP, and other echocardiographic data were also obtained. W_1 was enhanced in the MR group before surgery compared with the normal group (10.7 ± 5.7 vs $8.5 \pm 3.6 \times 10^3$ mmHg m/s³, $p < 0.05$). However, the results of two-way ANOVA showed this enhancement of W_1 was observed only in the subgroup of MR before surgery with lower arterial stiffness ($\beta < 13$, $p < 0.0001$). ERO, β and LAVI were predictor variables before surgery to determine RVSP. EF and ($Q-W_1$)_{st} before surgery were predictor variables for EF after surgery.

Conclusions: In the MR group before surgery, increased arterial stiffness suppresses compensatory enhancement of W_1 , and increases RVSP. Prolonged ($Q-W_1$)_{st} has the potential for predicting low EF after surgery.

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1. Introduction

Aged patients with nonischemic mitral regurgitation (MR) due to the flail leaflet were reported to suffer for excess rate of mortality in comparison with that expected in age-peer general population, but this rate difference between younger MR patients and younger general population did not show statistical significance [1]. The presumed causes are increased left ventricular (LV) myocardial

stiffness, reduced left atrial (LA) function, higher rate of complicated atrial fibrillation (AF), and increased right ventricular systolic pressure (RVSP) in aged patients [1–3]. However, since arterial stiffness increases with age inevitably, the effects of increased arterial stiffness on ventriculo-arterial interaction relevant to the ejection performance in MR should also be taken into consideration.

Wave intensity (WI) is a hemodynamic index obtained from an arterial site, which provides quantitative information about the dynamic behavior of the heart and the vascular system and their interaction [4–6]. The noninvasive measuring system of WI also provides arterial stiffness parameters [6]. We used WI analysis for elucidating the effects of increased arterial stiffness on cardiac performance and RVSP in severe MR, and for predicting ejection fraction (EF) after surgery.

* Corresponding author at: Department of Medical Engineering, Tokyo City University, 1-28-1 Tamazutsumi, Setagaya, Tokyo 1588557, Japan.
E-mail address: niki@bme.tcu.ac.jp (K. Niki).

2. Methods

2.1. Study population

We studied 121 consecutive patients with non-ischemic chronic MR (71 men, age 54 ± 15 years) who underwent surgical treatment for MR. Twenty-three subjects were excluded because of concomitant aortic valve disease ($n = 7$), mitral stenosis ($n = 4$), AF ($n = 6$), ischemic heart disease ($n = 3$), hypertrophic cardiomyopathy ($n = 1$) or aortic disease ($n = 2$), and the remaining 98 subjects were enrolled in the study. The study group included the patients with a history of hypertension ($n = 37$), hyperlipidemia ($n = 28$), diabetes mellitus ($n = 3$) and medication with angiotensin converting enzyme inhibitors or angiotensin II receptor antagonists ($n = 47$), diuretics ($n = 35$), calcium channel blockers ($n = 17$) and β -blockers ($n = 7$). Normal values of WI indices were obtained from 98 age-matched and gender-matched healthy participants (60 men, age 52 ± 14 years). All subjects provided informed consent, and the ethic committee of Sakakibara Heart Institute approved the study protocol.

2.2. Noninvasive measurements of WI and arterial stiffness

WI is given by

$$WI = (dP/dt)(dU/dt),$$

where dP/dt and dU/dt are the derivatives of pressure (P) and velocity (U) with respect to time [6]. Carotid arterial WI in a normal subject shows two sharp positive waves during a cardiac cycle, wave 1 and wave 2, which are generated by the left ventricle and divide ejection period into three phases (Fig. 1). Wave 1 occurring in early ejection (indicated by E in Fig. 1) corresponds to the forward travelling compression (pushing) waves, and the height of carotid arterial wave 1 (W_1) correlates with LV peak dP/dt [7]. The interval between the Q wave of the ECG and W_1 ($Q-W_1$) and the interval between W_1 and W_2 (W_1-W_2) are temporal indices which are used as surrogates for pre-ejection period and ejection time. Wave 2 is the forward travelling expansion (suction) wave generated by rapid fall in LV pressure [6,8,9].

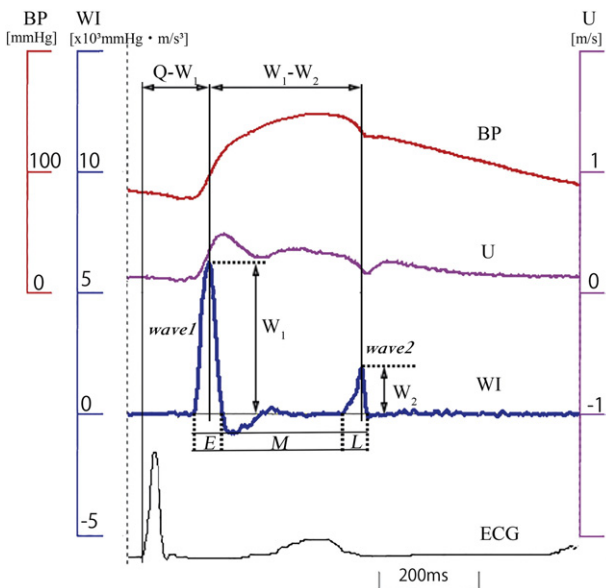


Fig. 1. Representative recordings of pressure (BP), blood flow velocity (U), and calculated wave intensity (WI) in the common carotid artery, and electrocardiogram (ECG) obtained from a normal subject. WI in a normal subject shows two sharp positive peaks during a cardiac cycle, wave 1 and wave 2, and the ejection period is divided into three phases (initial (E), mid (M) and late ejection (L)) by the two waves.

WI was obtained noninvasively with an ultrasonic system (SSD 6500, Hitach-Aloka, Tokyo, Japan) which simultaneously measures arterial diameter-change waveform by echo tracking and blood flow velocity by color Doppler. Arterial diameter-change waveform was calibrated by the upper arm blood pressure measured with a validated automated cuff-type sphygmomanometer (HEM-907, OMRON Healthcare Co., Ltd., Kyoto, Japan) immediately after the waveforms were obtained, and used as surrogates for blood pressure waveforms. By inputting the blood pressure data, WI indices and β were calculated automatically and waveforms and ECG were digitally recorded at an interval of 1 ms. The details and reproducibility of the system were described elsewhere [10]. This system measures the height of the two positive peaks (W_1, W_2), the interval between the peaks of the two waves (W_1-W_2) and the interval between the R wave of the ECG and W_1 ($R-W_1$). To measure the precise interval from the onset of the QRS complex of ECG to the peak of wave 1 ($Q-W_1$), we used custom software written in our laboratory retrieving stored text file data of WI.

The WI measuring system also calculates the carotid arterial stiffness parameter β [11], which is defined as follows:

$$\beta = \ln(Ps/Pd)/[(Ds-Dd)/Dd],$$

where, Ps and Pd are systolic and diastolic pressure (mm Hg) and Ds and Dd are the maximum and minimum diameters (mm) of the carotid artery in a cardiac cycle, respectively.

2.3. Echocardiography

Echocardiographic evaluation was performed in MR subjects using an echo machine (SONOS 7500; Philips Healthcare, MA, USA) according to the recommendations of the American Society of Echocardiography [12]. LV end-diastolic and end-systolic volume index (LVEDVI and LVESVI), LA volume index (LAVI) were determined using the modified Simpson's method. LA volume was measured at the end-systole just before the mitral valve opening. RVSP was obtained by adding the systolic tricuspid pressure gradient calculated by the modified Bernoulli equation and right atrial pressure [13]. Early filling (E) and atrial contraction filling (A) velocities of transmitral flow were measured using pulsed Doppler, and tissue Doppler velocity of the septal mitral annulus in early diastole (e') was also obtained from the apical four-chamber view. MR severity was quantified as averaged effective regurgitant orifice area (ERO) obtained by the Doppler volumetric method and proximal isovelocity surface area (PISA) method [14]. Regurgitant volume (RegV) and Regurgitant fraction (RegF) were calculated as $RegV = (\text{mitral stroke volume}) - (\text{aortic stroke volume})$, and $RegF = RegV/(\text{mitral stroke volume})$, respectively.

2.4. Measurement protocol

Measurements were performed before and early after surgery. After 15 min rest, WI data were acquired from the left common carotid artery at about 2 cm proximal to the carotid bulb. The transducer was held in place by a stereotactic clamp (Point setter, Mitaka Kohki, Co., Ltd., Tokyo, Japan) to avoid the movement of the observer. The measurements were performed three times and averaged data was used for analysis. Echocardiography was performed according to routine practice by skilled sonographers without knowledge of WI data.

2.5. Statistical analysis

Results were expressed as mean value \pm SD (standard deviation). Comparisons among groups were performed by Student's t -test or ANOVA, followed by Bonferroni or Dunnett test when necessary. To evaluate the relationship between WI indices or echocardiographic indices and β , Pearson's product-moment correlation was used. Each of the MR groups before surgery, after surgery and the normal group

Table 1
Clinical characteristics.

	MR (n = 98)	Normal (n = 98)
Age [years]	52 ± 14	52 ± 14
Gender [men/women]	60/38	60/38
Height [m]	1.65 ± 0.10	1.64 ± 0.10
Weight [kg]	61 ± 12	61 ± 11
BSA [m ²]	1.66 ± 0.20	1.67 ± 0.18

MR, mitral regurgitation; BSA, body surface area.

was subdivided into two groups with higher β and with lower β at the median value of β in the MR group before surgery, and the two-way ANOVA was applied to the evaluation of the association of W₁ with β. Univariate linear regression analyses were performed for the data obtained before surgery relating RVSP before surgery and EF after surgery. Then, the variables which were correlated with RVSP before surgery and EF after surgery (p ≤ 0.1) were entered into step wise multivariate linear regression models. To yield the threshold value of predictor variable separating a clinical diagnosis that EF after surgery ≤ 50% from one that EF after surgery > 50%, the receiver-operator characteristic (ROC) curves were created, and the optimal combinations of sensitivity and specificity were chosen. A p value < 0.05 was set for statistical significance. Statistical analyses were performed using SPSS version 21 (IBM Corp., Armonk, NY, USA). GraphPad Prism 5.01 (GraphPad Software Inc., CA, USA) was used for the two-way ANOVA.

3. Results

3.1. Population characteristics

There were no significant differences between the MR group and the normal group except systolic and diastolic pressures, which were lower in the MR (Tables 1, 2). None of the patients as well as healthy subjects had a significant carotid arterial stenosis. Valve repair was performed in 90 patients and replacement in 8 patients successfully. The underlying etiology of MR was fibroelastic degeneration (n = 83), billowing leaflets (n = 2), Barlow's disease (n = 4), healed infective endocarditis (n = 5), rheumatism (n = 3) or cleft (n = 1).

3.2. W₁ indices and arterial stiffness

Measurements after surgery were performed 8 ± 5 days after surgery. No in-hospital death was observed. The dependency of Q-W₁ and W₁-W₂ on heart rate (HR) were observed in the normal group (Q-W₁ = -0.51 HR + 167, r = 0.46, p < 0.0001; W₁-W₂ = -1.33 HR + 358, r = 0.68, p < 0.0001). According to Lewis et al. [15], the

Table 2
Wave intensity indices and arterial stiffness.

	MR		Normal
	Before surgery	After surgery	
W ₁ [× 10 ³ mm Hg m/s ³]	10.7 ± 5.7*	8.3 ± 3.7 ^ξ	8.5 ± 3.6 ^ξ
W ₂ [× 10 ³ mm Hg m/s ³]	0.8 ± 0.6**	2.4 ± 1.0 ^{ξξ}	1.9 ± 0.8 ^{ξξ}
(Q-W ₁)st [ms]	171 ± 16	189 ± 22 ^{**ξξ}	167 ± 10
(W ₁ -W ₂)st [ms]	330 ± 24**	320 ± 23 ^{**ξ}	357 ± 15 ^{ξξ}
β	13.6 ± 4.8*	13.7 ± 5.2*	11.6 ± 3.8 ^ξ
Systolic pressure [mm Hg]	110 ± 11**	102 ± 12 ^{**ξξ}	118 ± 12 ^{ξξ}
Diastolic pressure [mm Hg]	59 ± 10**	56 ± 8 ^{**ξ}	69 ± 9 ^{ξξ}
Heart rate [bpm]	65 ± 10	71 ± 12 ^{*ξ}	64 ± 10

W₁ indices (W₁, W₂, Q-W₁, W₁-W₂) are the same as Fig. 1; suffix st, see text; β, stiffness parameter.

* vs normal subjects (*p < 0.05, **p < 0.001), ξ vs before surgery (ξp < 0.05, ξξp < 0.001).

Table 3
Echocardiographic data and (Q-W₁)st before and after surgery in mitral regurgitation and correlation with β.

	Before surgery		After surgery	
		r		r
LVEDVI [ml/m ²]	89 ± 20	-0.30 ^ξ	61 ± 16**	-0.22 ^ξ
LVESVI [ml/m ²]	32 ± 10	-0.26 ^ξ	29 ± 12**	-0.16
EF [%]	64 ± 7	0.11	54 ± 9**	0.08
LAVI [ml/m ²]	78 ± 27	0.13	51 ± 17**	0.13
RVSP [mm Hg]	39 ± 15	0.36 ^{ξξ}	26 ± 6**	0.03
E/A	2.03 ± 0.77	-0.25 ^ξ	1.55 ± 0.77**	-0.26 ^ξ
E/e'	14.1 ± 6.0	0.43 ^{ξξ}	19.4 ± 6.9**	0.02
e'	9.7 ± 2.7	-0.57 ^{ξξ}	6.4 ± 1.8**	-0.21 ^ξ
ERO [cm ²]	0.48 ± 0.17	-0.11		
RegV [ml]	69 ± 16	-0.19		
RegF [%]	55 ± 8	0.11		
RegV/ERO [ml/cm ²]	152 ± 35	-0.02		
RegF/ERO [%/cm ²]	124 ± 34	0.23 ^ξ		
Reduction rate of RVSP [%]			25.6 ± 29.0	0.42 ^ξ
(Q-W ₁)st [ms]	171 ± 16	-0.14	189 ± 22**	0.01

LVED(S)VI, left ventricular end-diastolic (systolic) volume index; EF, ejection fraction; LAVI, left atrial volume index; RVSP, right ventricular systolic pressure; ERO, effective regurgitant orifice area; RegV, regurgitant volume; RegF, regurgitant fraction; W₁ indices (Q-W₁) is the same as Fig. 1; suffix st, see text; β, stiffness parameter; Reduction rate of RVSP = (RVSP before surgery - RVSP after surgery) / RVSP before surgery × 100; Comparison between before and after surgery *p < 0.05, **p < 0.001; r, correlation with β ξp < 0.05, ξξp < 0.001.

standardized indices were defined as follows,

$$(Q-W_1)st = 0.51 HR + Q-W_1,$$

$$(W_1-W_2)st = 1.33 HR + W_1-W_2.$$

As compared with the normal group, the MR group before surgery, as a whole, showed higher W₁, lower W₂, shorter (W₁-W₂)st, and higher β but the same level of (Q-W₁)st (Table 2). After surgery, W₁ decreased to the same level as the normal group. (W₁-W₂)st decreased further, and (Q-W₁)st increased. W₂ after surgery increased prominently, and became significantly higher as compared with the normal group. There was no change in β after surgery. β was significantly correlated

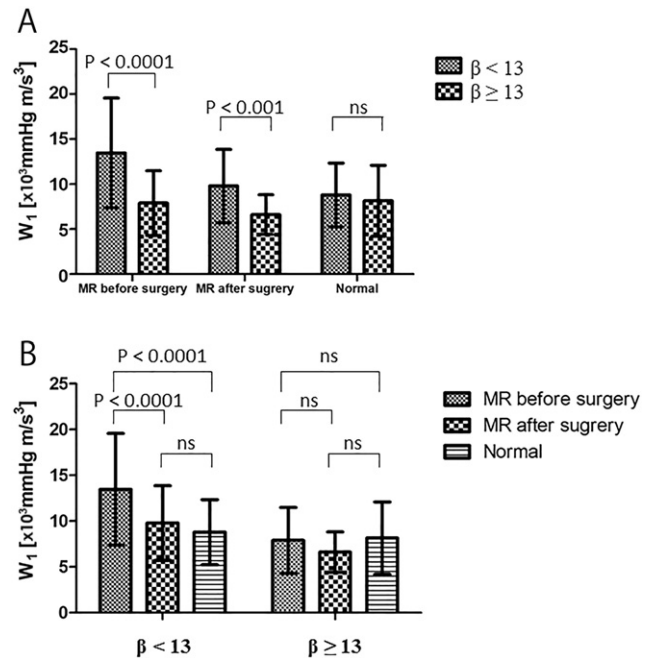


Fig. 2. (A) Comparisons of W₁ in the subgroups with lower and higher β in each of MR before surgery, MR after surgery, and normal groups. (B) Comparisons of W₁ in MR before surgery, MR after surgery, and normal in each subgroup with lower and higher β.

with age both in the MR group and the normal group ($r = 0.74$, $p < 0.001$, $r = 0.70$, $p < 0.001$, respectively). $(Q-W_1)_{st}$ did not correlate with β in MR before and after surgery (Table 3), though the correlation between $(Q-W_1)_{st}$ and β in the normal group was significant ($r = -0.23$, $p = 0.02$).

The results of two-way ANOVA show, in detail, how W_1 varied with the difference in β in the MR group (Fig. 2). The median value of β in the MR group before surgery was 12.8. In the MR before surgery group, the patients with lower β (<13) had considerably higher W_1 than the patients with higher β (≥ 13) (mean value: 13.5 vs 7.9×10^3 mm Hg m/s^3) (Fig. 2A). In the MR after surgery group, the difference in W_1 between the subgroups with lower and higher β decreased (9.8 vs 6.6×10^3 mm Hg m/s^3), although the difference was still significant. While in the normal group, there was no difference in W_1 between the subgroups with lower and higher β . Among the subgroups with lower β , MR before surgery had significantly higher W_1 compared with MR after surgery and normal (13.5 , 9.8 , 8.8×10^3 mm Hg m/s^3 , respectively). While there were no differences in W_1 among the subgroups with higher β (Fig. 2B).

3.3. The relationships between echocardiographic indices and β or W_1 in MR

The LVEDVI, E/A, e' were correlated with β before and after surgery (Table 3). LVESVI, RVSP, E/ e' were correlated with β before surgery, but not after surgery. Though RVSP did not correlate with β after surgery, the reduction rate of RVSP after surgery was correlated with β . Since RegV and RegF increased with increase in ERO ($r = 0.57$, $p < 0.0001$; $r = 0.49$, $p < 0.0001$, respectively), these were normalized as RegV/ERO and RegF/ERO. Only RegF/ERO was correlated with β . W_1 was correlated with LVEDVI before surgery ($r = 0.26$, $p = 0.01$).

3.4. Determinants of RVSP before surgery and EF after surgery

Univariate and following stepwise multivariate regression analyses showed ERO, β and LAVI were selected independent predictor variables to determine RVSP before surgery (Table 4). Meanwhile, EF and $(Q-W_1)_{st}$ before surgery were selected predictor variables for the response variable EF after surgery (Table 5). The ROC curve was constructed to define optimal cut-off in $(Q-W_1)_{st}$ to predict low EF after surgery ($\leq 50\%$). The selected cut-off value was 180 ms, which gave a sensitivity of 57% and a specificity of 88% (area under ROC 0.72, $p = 0.001$) (Fig. 3A). On the other hand, the cut-off value of EF before surgery, 60%, gave a sensitivity of 90% and a specificity of

Table 4
Results of univariate and multivariate linear regression analyses for determinants of right ventricular systolic pressure before surgery.

Variables before surgery	Univariate analysis		Multivariate analysis $R^2 = 0.34$ (adjusted $R^2 = 0.31$, $p < 0.001$)		
	r	p	Beta	p	VIF
W_1	-0.21	0.039	-0.11	0.283	1.381
W_2	0.05	0.658			
β	0.36	<0.001	0.35	<0.001	1.025
$(Q-W_1)_{st}$	-0.08	0.440			
LVEDVI	0.15	0.145			
LVESVI	0.14	0.169			
EF	-0.02	0.853			
LAVI	0.31	0.003	0.20	0.031	1.062
E/A	0.08	0.459			
e'	-0.29	0.004	-0.17	0.114	1.620
ERO	0.36	<0.001	0.37	<0.001	1.039

WI indices (W_1 , W_2 , $Q-W_1$) are same as Fig. 1; suffix st, see text; LVED(S)VI, left ventricular end-diastolic (systolic) volume index; EF, ejection fraction; LAVI, left atrial volume index; ERO, effective regurgitant orifice area; Beta, standardized coefficients; VIF, variance inflation factor.

Table 5
Results of univariate and multivariate linear regression analyses for determinants of EF after surgery.

Variables before surgery	Univariate analysis		Multivariate analysis $R^2 = 0.34$ (adjusted $R^2 = 0.32$, $p < 0.001$)		
	r	p	Beta	p	VIF
Age	0.27	0.008	0.04	0.657	1.193
W_1	0.08	0.449			
W_2	-0.15	0.154			
β	0.02	0.832			
$(Q-W_1)_{st}$	-0.52	<0.001	-0.39	<0.001	1.274
LVEDVI	-0.27	0.007	-0.14	0.106	1.097
EF	0.47	<0.001	0.28	0.004	1.274
LAVI	-0.10	0.353			
E/A	-0.21	0.041	-0.14	0.101	1.017
e'	0.02	0.862			
RVSP	-0.10	0.338			

WI indices (W_1 , W_2 , $Q-W_1$) are same as Fig. 1; suffix st, see text; LVEDVI, left ventricular end-diastolic volume index; EF, ejection fraction; LAVI, left atrial volume index; RVSP, right ventricular systolic pressure; Beta: standardized coefficients; VIF, variance inflation factor.

55% for predicting reduced EF after surgery ($\leq 50\%$) (area under ROC 0.71, $p = 0.001$) (Fig. 3B). Furthermore, among the subgroup with EF before surgery $\leq 60\%$ ($n = 25$), the cut-off value of $(Q-W_1)_{st}$ 180 ms gave a sensitivity of 81% and a specificity of 89% for predicting reduced EF after surgery ($\leq 50\%$) (area under ROC 0.87, $p = 0.003$) (Fig. 3C).

4. Discussion

The present study evaluated the characteristics of arterial stiffness and wave intensity indices in MR and found that in the MR group before surgery, increased arterial stiffness is accompanied by suppressions of compensatory enhancement of ejection performance and increases RVSP. Furthermore, prolonged $(Q-W_1)_{st}$, a surrogate for pre-ejection period, has the potential for predicting low EF after surgery.

4.1. Use of the stiffness parameter β as an index of arterial stiffness

Most of the studies evaluated arterial stiffness by measuring pulse wave velocity (PWV: c). Conventional methods of measuring c have been based on two-point measurements, i.e., measurements of the time of travel of the wave over a known distance. Therefore, c measured over a relatively long distance is integration of regional c in each artery involved within that range. On the other hand, carotid arterial stiffness parameter β is measured at one point. Thus, changes in β may not represent the overall changes in arterial stiffness. Nevertheless, the Swiss SAPALDIA cohort study reported the strong correlation ($r^2 = 0.49$, $p < 0.001$) between brachial-ankle PWV and carotid arterial distensibility coefficient defined as $[(Ds - Dd^2)/Dd^2]/(Ps - Pd)$, which is approximately the inverse of β [16]. Consequently, we consider that changes in carotid arterial β are associated with changes in β of other large arteries.

As an index of arterial stiffness, β has the advantage that it does not depend on pressure, while PWV decreases with a decrease in pressure. In our study, systolic and diastolic pressures were lower in the MR before surgery than the normal group, and the pressures decreased further after surgery. For this reason, we needed an index to evaluate arterial stiffness without regard to difference in pressure. β satisfies this requirement.

4.2. The enhancement of W_1 in the wave intensity in MR before surgery

WI analyses assert that during the period of wave 1, effects of reflected waves are negligible and the contours of pressure and velocity

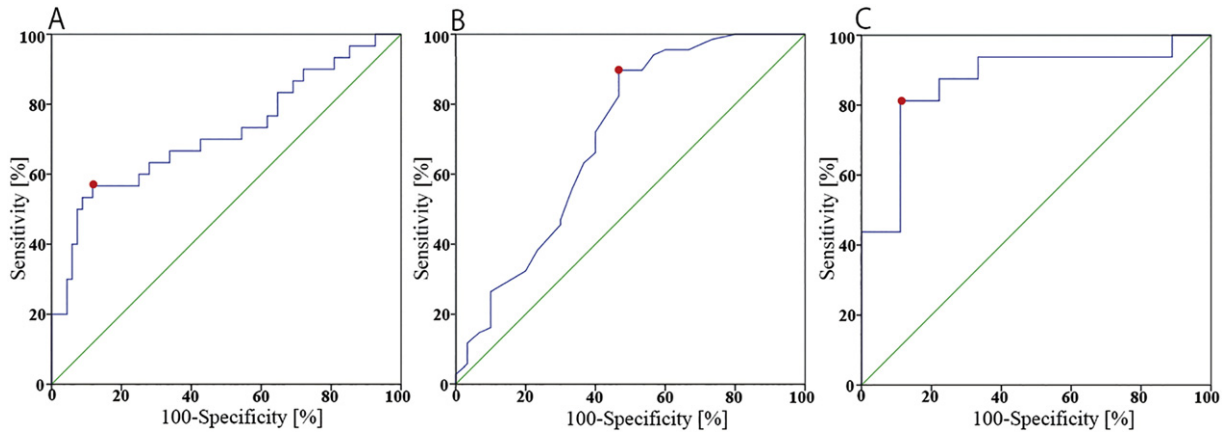


Fig. 3. Receiver-operator characteristic curves and selected combinations of sensitivity and specificity (red dots) to predict EF after surgery $\leq 50\%$. (A) Cut-off value of $(Q-W_1)_{st}$ before surgery = 180 ms, (B) Cut-off value of EF before surgery = 60% and (C) Cut-off value of $(Q-W_1)_{st}$ before surgery = 180 ms in the subgroup of patients with EF before surgery $\leq 60\%$.

waves are dominated by forward waves only [4,6]. Under such conditions, the following relation holds:

$$P(t) - P_{ed} = \rho c U(t) \quad (1)$$

where $P(t)$ and $U(t)$ are aortic pressure and velocity at any time t during the period of wave 1, P_{ed} is aortic end-diastolic pressure, ρ and c are the blood density and the pulse wave velocity [9]. Though ρc looks like resistance to flow, $U(t)$, and is sometimes called “characteristic impedance” [17], it has no relation to the viscous systemic resistance. Nevertheless, ρc plays the role of afterload which the left ventricle encounters during initial ejection. By the use of Eq. (1), the relation $WI = (dP/dt)(dU/dt) = (dP/dt)^2/\rho c$ is obtained, which yields the following relation:

$$\text{Peak of } WI(W_1) = (A_o \text{ peak } dP/dt)^2/\rho c \quad (2)$$

where A_o peak dP/dt is the maximum rate of rise in aortic pressure. A_o peak dP/dt is approximately equal to the maximum rate of LV pressure rise (LV peak dP/dt) unless aortic stenosis exists [18]. Thus, WI , which is an index obtained from arterial site, is related to LV peak dP/dt . Although the carotid artery is apart from the aorta, the correlation between carotid arterial W_1 and LV peak dP/dt was also confirmed by clinical measurements [7]. LV peak dP/dt is an isovolumic contraction phase index. However, there is no isovolumic contraction phase in the presence of MR, hence LV peak dP/dt may not reflect the myocardial contractile state. Nevertheless, LV peak dP/dt was reported to be insensitive to changes in afterload and sensitive to acute changes in contractility in MR patients [19]. Thus, it is of practical use for assessing directional changes in the myocardial contractile state in MR, though it is affected by changes in preload (i.e. LVEDVI).

4.3. Characteristics of wave intensity in MR and the effects of increased arterial stiffness on cardiac performance

The enhancement of W_1 in the MR before surgery is a manifestation of the mechanism of the left ventricle to compensate for the development of MR, though the enhancement was observed only in lower arterial stiffness group. The compensation is made mainly by increasing LVEDV, i.e. preload, and using the Frank-Starling mechanism. There are several factors to modify this mechanism: changes in preload, myocardial properties, and afterload. The associations of the increase in β with these factors have not been well-documented, but should deserve careful consideration.

Firstly, LVEDV is enlarged by MR, but the degree of enlargement may be affected by the diastolic property of the myocardium. Roman et al. reported that β was negatively associated with LV end-diastolic chamber diameter [20], and Wohlfahrt et al. reported that increase in arterial stiffness plays an important role in LV stiffening during diastole [21]. In our study, β was correlated with LVEDVI without correlation with ERO in MR before surgery. Therefore, the diastolic LV stiffening is considered to cause a decrease in preload, and causes a decrease in LV peak dP/dt , hence W_1 . Secondly, LV peak dP/dt is a sensitive index to assess LV contractile strength. However, it can be obtained only by catheterization. Meanwhile, preejection period (PEP) is obtained noninvasively, and its shortening is entirely attributed to an increase in LV peak dP/dt [15]. WI analysis gives a surrogate for PEP, namely $(Q-W_1)_{st}$. It is reported that ventricular systolic stiffening progresses in association with arterial stiffening, and increases LV contractile strength (LV peak dP/dt) [22]. Certainly, $(Q-W_1)_{st}$ in the normal group was negatively correlated with β . However, in the MR group, $(Q-W_1)_{st}$ did not correlate with β , which means that the expected ventricular systolic stiffening did not bring about positive inotropic effect. Finally, according to Eq. (1), ρc works as afterload during early ejection. Ejection velocity $U(t)$ generated by pressure rise $[P(t) - P_{ed}]$ is in inverse proportion to ρc . W_1 is an index of ejection performance related to ventriculo-arterial interaction, and as Eq. (2) shows, increase in c , hence β , decreases W_1 . In normal subjects, increased LV systolic stiffening may cover negative effect of β on W_1 . This is considered to be the reason why β did not correlate with W_1 in the normal group. However, the expected ventricular systolic stiffening did not emerge in MR.

Thus, in association with increase in β in MR, LV diastolic stiffening limited compensatory enlargement of LVEDV, and LV systolic stiffening did not occur, and afterload ρc increased. These observations support our assertion that compensatory enhancement of W_1 is not observed in MR with increased β .

The wave 2 is a suction wave generated by the left ventricle as a consequence of both the decline in tension bearing ability of cardiac muscle and the inertial force of aortic blood flow near the end-ejection [6,8]. We reported elsewhere that the maximum value, W_2 , of the wave 2 is reduced in MR using another ultrasonic system [9]. In this study, W_2 was also reduced and the height of W_2 recovered after the repair of regurgitation.

4.4. The effects of arterial stiffness on pulmonary hypertension (PH)

The PH in MR emerges through multifactorial processes. In this study, patients with decompensated heart failure or EF lower than

40% were not included, which indicated systolic dysfunction was not the major cause of PH in this group.

ERO, LAVI and β were independent determinants of RVSP before surgery. The increase in β increases LV afterload during initial ejection, and augments RegF/ERO, which would cause increase in left atrial pressure during systole and RVSP. After surgery, the strong correlation between RVSP and β disappeared, and the reduction rate of RVSP by surgery increased with increase in β , which suggests that the surgical treatment had more beneficial effect of improving PH in MR with higher β than with lower β . Surgical therapy was associated with reduced long term mortality in older patients [1]. However, the long term prognosis of surgically treated MR patients with PH, which included more aged patients, was still worse than that of patients without PH [23]. Murashita et al. reported that preoperative PH disappeared after surgery in degenerative MR patients, and the leading cause of cardiovascular death after surgery was stroke, and most of patients who had recurrence of PH suffered from AF, which suggested recurrent PH after surgery was caused by different pathophysiology due to PH before surgery [24].

4.5. Usefulness of W_1 indices in predicting EF after surgery

$(Q-W_1)_{st}$ was an index with higher specificity to predict EF after surgery than the preoperative EF. Strictly speaking, $Q-W_1$ is the sum of PEP, the time of travel of the pulse wave over the distance from the LV to the carotid artery and the time from the beginning of ejection to the peak of wave 1.

In MR, EF before surgery is still a major independent determinant of long-term outcome under surgical treatment and the best outcome is achieved when surgical treatment is considered before EF decreases to a level under 60% [25]. Since EF is an index indicating the balance between cardiac contractility (e.g. Emax) and afterload (e.g. effective arterial elastance), it is not a measure of myocardial function per se [26], and the cut off value of EF 60% before surgery showed high sensitivity but rather low specificity for predicting reduced EF after surgery (Fig. 3(b)). LV systolic dimension is an additional index to reinforce the accuracy of prediction for post-operative EF [27,28]. However, since LVESVI was affected by β , temporal indices such as PEP and its surrogate $Q-W_1$ are considered to be more suitable additional indices in MR with higher arterial stiffness. PEP is an old concept, but its high sensitivity and reproducibility is still useful in indicating early reduction of an intrinsic property of the myocardium. By using both indices ($(Q-W_1)_{st} > 180$ ms and $EF < 60\%$), prediction of low EF after surgery with higher sensitivity and specificity is possible.

4.6. Noninvasive measurement of W_1

We evaluated the relationship between pressure and diameter-change waveforms in the human carotid artery and showed the similarity [29]. To use a diameter-change waveform as a surrogate for a blood pressure waveform, brachial arterial systolic and diastolic pressures were used for calibration. The so-called amplification of pressure in the upper arm in young adults is considerable. However, in the elderly, augmentation of aortic pressure caused by early return of reflected waves from the lower body becomes prominent, which increases aortic peak pressure, and eventually makes the difference between aortic peak pressure and upper arm peak pressure less significant [30].

Because of the incompressibility of arterial wall, $(D_s - D_d)/D_d$ is greater for an inner layer (e.g. intima) than for an outer layer (e.g. adventitia) of arterial wall. Therefore, β is smaller for an inner layer than for an outer layer. We obtained β by setting the positions for echo tracking in the adventitia for the following reasons: 1) It is easier to obtain stable tracking. 2) The PWV calculated from the β obtained from the adventitia agrees well with the PWV obtained by a different method [31].

5. Limitations

This study was a single center study and number of subjects was not large. The patients were limited to those who agreed on surgical treatment. Patients with decompensated heart failure or EF lower than 40% were not included, which may have changed characteristics of the patients with PH.

6. Conclusions

In MR before surgery, cardiac contractility is enhanced to compensate for the reduction in pressure generating ability of the left ventricle due to regurgitation. However, compensatory enhancement of cardiac contractility was observed only in MR with lower β . With the increase in β , cardiac performance of MR patients before surgery deteriorates and RVSP increases progressively. Since arterial stiffness is not improved by vasodilator or diuretics, such medication is not so effective for improving cardiac performance and decreasing PH associated with increased arterial stiffness. While surgical correction of MR improves the cardiac performance and decreases PH markedly. Prolonged $(Q-W_1)_{st}$ has the potential for predicting low EF after surgery.

Conflict of interest

None declared.

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