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Evaluation of the Effect of Increased Arterial Stiffness on Ejection Performance and Pulmonary Arterial Pressure in Primary Mitral Regurgitation and Prediction of Ejection Fraction after Surgery: Analysis Using Wave Intensity

Kiyomi Niki and Motoaki Sugawara

Abstract

Mitral regurgitation (MR) is a common valvular disorder that has important health consequences. Surgical therapy is associated with reduced long-term mortality in elder patients. Several guidelines exist regarding when and in whom to perform mitral valve surgery, but they are controversial. It is essential to obtain preoperative indices that are promising for predicting postoperative left ventricular function and right ventricular pressure correctly. In aged MR patients, various hemodynamic conditions are presumed to be the causes of higher rate of mortality. In addition, aging causes increase in arterial stiffness. Therefore, it is also important to consider the effects of increased arterial stiffness on hemodynamics in MR. This review was written on the basis of our studies of wave intensity and will focus on the effects of increased arterial stiffness with a specific emphasis on wave intensity, which provides quantitative information about hemodynamic interaction between the ventricle and the arterial system.

Keywords: mitral regurgitation, arterial stiffness, wave intensity, surgical treatment, pulmonary hypertension

1. Introduction

A recent study reported that the rate of mortality among MR patients aged from 65 years upwards is higher compared with that expected among the general population, though the difference between younger MR patients and the general population is not significant [1]. Differences in age among the study groups are considered to yield different outcomes of a therapeutic strategy for treating severe

MR [2, 3]. The causes of the differences are considered to be reduced left atrial (LA) function and higher rate of complicated atrial fibrillation (AF) and increased ventricular myocardial stiffness in aged patients [2]. In addition to these factors, we consider that the effects of increased arterial stiffness, namely ventriculo-arterial coupling, are important.

The employed ultrasonic system provides arterial stiffness parameters and wave intensity (WI), which gives quantitative information about the dynamic behavior of the heart interacting with the vascular system [4–6]. Using indices obtained from measurements of wave intensity noninvasively, we analyzed the effects of changes in arterial stiffness on left ventricular (LV) performance and right ventricular pressure in MR and proposed a predictor of ejection fraction (EF) after surgery [7].

2. What is wave intensity?

Wave intensity (WI) is a hemodynamic index. It can be defined at any site in the circulatory system and evaluates the working condition of the heart interacting with the arterial system. WI is given by

$$WI = (dP/dt)(dU/dt), \tag{1}$$

where dP/dt and dU/dt are the time derivatives of pressure (P) and velocity (U) [6]. In a major artery of a healthy subject, two sharp positive peaks of WI are apparent during a cardiac cycle: wave 1 and wave 2 (**Figure 1**). Wave 1 occurs in early ejection and wave 2 occurs near end-ejection. The characteristics of these waves are theoretically described in the following way. According to the general theory of pulse waves traveling in an artery, the rates of changes in pressure and flow velocity at a fixed point caused by a forward wave and a backward (reflected) wave are related as follows, respectively:

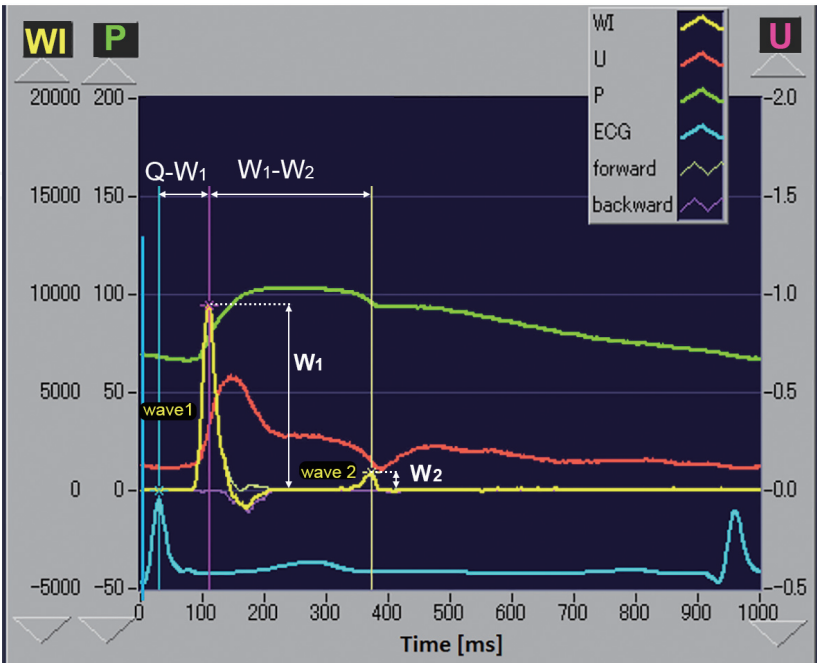


Figure 1. Representative recordings of pressure P (mm Hg), blood flow velocity U (m/s), and calculated wave intensity WI (mm Hg m/s³) and electrocardiogram ECG obtained from a healthy subject. WI in a healthy subject shows two sharp peaks during a cardiac cycle, wave 1 and wave 2. Forward: forward wave component, backward: backward wave component.

for a forward wave,

$$dP_f/dt = \rho c dU_f/dt \quad (2)$$

for a backward wave,

$$dP_b/dt = -\rho c dU_b/dt. \quad (3)$$

Here, dP_f/dt and dU_f/dt are the rates of changes in pressure and velocity caused by a forward wave, and dP_b/dt and dU_b/dt are those caused by a backward wave, respectively; ρ is the blood density, and c is the pulse wave velocity [8]. The actual measured rates of changes in pressure and velocity, dP/dt and dU/dt , are the sum of the rate of changes caused by a forward and a backward wave:

$$dP/dt = dP_f/dt + dP_b/dt, \quad (4)$$

$$dU/dt = dU_f/dt + dU_b/dt. \quad (5)$$

Using the above four equations, we can write WI as follows:

$$WI = (dP/dt)(dU/dt) = [(dP_f/dt)^2 - (dP_b/dt)^2] / \rho c = \rho c [(dU_f/dt)^2 - (dU_b/dt)^2]. \quad (6)$$

If $WI > 0$, the rates of changes caused by the forward wave, dP_f/dt and dU_f/dt , are greater than those caused by the backward wave, dP_b/dt and dU_b/dt , and vice versa. During the periods of wave 1 and wave 2, $WI > 0$ definitely, and dP_b/dt and dU_b/dt are nearly equal to zero [9]. The characteristics of these two positive waves are different. Wave 1 is associated with acceleration and an increase in pressure; thus it is a compression (pushing) wave. Wave 2 is associated with deceleration and a decrease in pressure and is therefore an expansion (suction) wave (**Figure 1**). The existence of suction wave near end-ejection was a surprising finding by Parker et al. [10], because it means that the left ventricle actively stops forward blood flow.

According to the description above, WI during the periods of wave 1 and wave 2 can be written as

$$WI = (dP_f/dt)^2 / \rho c. \quad (7)$$

Thus, the peak values of dP_f/dt will give the peak values of WI, that is, W_1 and W_2 . During the period of wave 1, the peak value of dP_f/dt in the artery concerned is necessarily related to peak value of dPA/dt (peak dPA/dt), where PA is aortic pressure. It has been confirmed experimentally that peak dPA/dt is approximately equal to LV peak dP/dt [8]. Therefore, W_1 can be written as

$$W_1 \propto (LV \text{ peak } dP/dt)^2 / \rho c. \quad (8)$$

During the period of wave 2, it has been reported that negative peak dP_f/dt is in proportion to the negative maximum value of $\rho c dU_f/dt$, that is, ρc times the maximum rate of deceleration (negative max dU_f/dt) [11].

Therefore, W_2 can be written as

$$W_2 \propto (\rho c \text{ negative max } dU_f/dt)^2 / \rho c = \rho c (\text{negative max } dU_f/dt)^2 \quad (9)$$

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 used as surrogates for pre-ejection period and ejection time (**Figure 1**).

3. Noninvasive measurements of wave intensity and arterial stiffness

WI in major arteries is obtained noninvasively with a WI measuring system incorporated in ultrasonic diagnostic equipment, which measures arterial diameter-change waveform by echo tracking and blood flow velocity by color Doppler. Arterial diameter-change waveform is used as a surrogate for a blood pressure waveform [12] (see Appendix A.4). Henceforward, we will focus particularly on carotid arterial WI.

The WI measurement system also calculates the two arterial elastic moduli, stiffness parameter β [13] and pressure strain elastic modulus E_p , which are defined as follows:

$$\beta = \ln (P_s/P_d)/[(D_s - D_d)/D_d]$$

and

$$E_p = k(P_s - P_d)/[(D_s - D_d)/D_d],$$

where, P_s and P_d are systolic and diastolic pressures (mm Hg) and D_s and D_d are the maximum and minimum diameters (mm) of the carotid artery during a cardiac cycle, respectively. $k = 0.133$ (kPa/mm Hg), which is the factor for converting mmHg to kPa (10^3 N/m²).

4. Relationship between wave intensity and arterial stiffness in healthy subjects

According to Eq. (8), W_1 is in inverse proportion to c . It is known that c increases with β [14]. Therefore, W_1 is expected to decrease with an increase in β if LV peak dP/dt and β change independently of each other. However, ventriculo-arterial couplings concerning the relation between changes in cardiac contractility (say peak dP/dt) and arterial stiffness (say β) have been reported. According to Kass D [15], age-related arterial stiffening is matched by ventricular systolic stiffening (increase in E_{max}), maintaining arterial-heart interaction age-independent. Indeed, our measurements in healthy subjects showed that changes in W_1 did not correlate with changes in β (Figure 2a).

5. Measurements of wave intensity in patients with MR and in healthy subjects

5.1 Population characteristics

We studied 98 consecutive patients with nonischemic chronic MR (60 men, age 52 ± 14 years) who underwent surgical treatment for MR and 98 age-matched and gender-matched healthy participants (60 men, age 52 ± 14 years) without any known cardiac disease, who were normotensive and had no history of serious noncardiac disease [7]. Informed consent was obtained from each subject, and the study protocol was approved by the ethics committee of Sakakibara Heart Institute. The characteristics of our study population are summarized in Table 1. There were no significant differences in hemodynamic data between the MR group and the healthy group except systolic and diastolic pressures, which were lower in the MR (Table 2). The etiologies of MR were as follows. Fibroelastic degeneration ($n = 83$), billowing leaflets

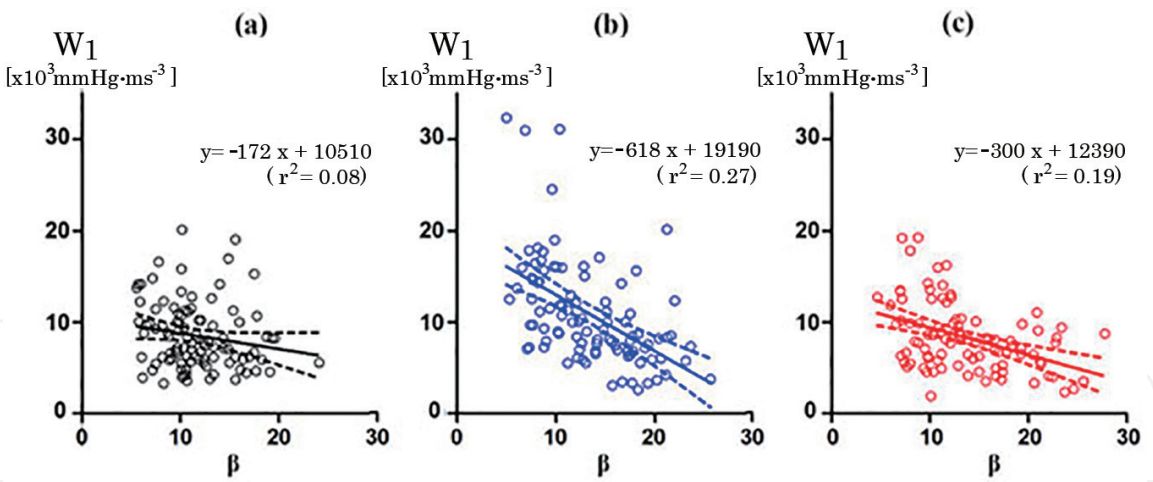


Figure 2. Relations between W_1 and β in (a) healthy control group, (b) MR group before surgery, and (c) MR group after surgery. The solid lines show the regression line. The slope of the regression line in (a) does not significantly deviate from zero ($p = 0.08$). The slope of the regression line in (b) deviates from zero significantly ($p < 0.0001$). The difference in the slope of regression line between (a) and (c) is not significant ($p = 0.65$).

	MR subjects	Healthy control
Number	98	98
Age (years)	52 ± 14	52 ± 14
Sex (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.

Table 1. Clinical characteristics [7].

($n = 2$), Barlow's disease ($n = 4$), healed infective endocarditis ($n = 5$), rheumatism ($n = 3$), or cleft ($n = 1$). The surgical therapies (valve repair in 90 patients and replacement in 8 patients) were performed successfully in all patients. Representative recordings of WI before and after surgery are shown in **Figure 3**. β was highly significantly correlated with age both in the MR group and the healthy group ($r = 0.74$, $p < 0.001$; $r = 0.70$, $P < 0.001$, respectively). W_1 was not correlated with β in the healthy group (goodness of fit $R^2 = 0.02$, $p = 0.08$) (**Figure 2a**) as mentioned above.

5.2 Effects of increased arterial stiffness on wave intensity in MR before and after surgery

The MR group before surgery showed higher W_1 , and unlike the healthy group, W_1 was correlated with β in MR group before surgery ($R^2 = 0.26$, $p < 0.0001$) (**Figure 2b**). To elucidate this relationship, it is necessary to give full consideration to the particular ejection dynamics of MR, that is, simultaneous ejection to the aorta and the left atrium. Regurgitation (ejection to the left atrium) is accompanied by increase in preload (LVEDVI), which enhances LV peak dP/dt , hence W_1 . Contrary to this, increase in β is reported to be associated with a decrease in LV end-diastolic chamber diameter [16], which decreases preload, hence W_1 . Wohlfahrt et al. [17] also reported that

	MR		Healthy control
	Before surgery	After surgery	
W_1 ($\times 10^3 \text{ mm Hg} \cdot \text{m/s}^3$)	$10.7 \pm 5.7^*$	$8.3 \pm 3.7^{\xi}$	$8.5 \pm 3.6^{\xi}$
W_2 ($\times 10^3 \text{ mm Hg} \cdot \text{m/s}^3$)	$0.8 \pm 0.6^{**}$	$2.4 \pm 1.0^{*\xi\xi}$	$1.9 \pm 0.8^{\xi\xi}$
$(Q-W_1)\text{st}$ (ms)	171 ± 16	$189 \pm 22^{*\xi\xi}$	167 ± 10
$(W_1-W_2)\text{st}$ (ms)	$330 \pm 24^{**}$	$320 \pm 23^{*\xi}$	$357 \pm 15^{\xi\xi}$
β	$13.6 \pm 4.8^*$	$13.7 \pm 5.2^*$	$11.6 \pm 3.8^{\xi}$
E_p (kPa)	149 ± 58	141 ± 58	142 ± 50
P_s (mm Hg)	$110 \pm 11^{**}$	$102 \pm 12^{*\xi\xi}$	$118 \pm 12^{\xi\xi}$
P_d (mm Hg)	$59 \pm 10^{**}$	$56 \pm 8^{*\xi}$	$69 \pm 9^{\xi\xi}$
HR (bpm)	65 ± 10	$71 \pm 12^{*\xi}$	64 ± 10

*WI indices (W_1 , W_2 , $Q-W_1$, and W_1-W_2) are the same as Figure 1; suffix st, see text; β , stiffness parameter; E_p , pressure strain elastic modulus; P_s , systolic blood pressure; P_d , diastolic blood pressure; HR, heart rate.
*vs. healthy subjects ($^*p < 0.05$, $^{**}p < 0.001$); $^{\xi}$ vs. before surgery ($^{\xi}p < 0.05$, $^{\xi\xi}p < 0.001$).*

Table 2.
WI indices and arterial stiffness [7].

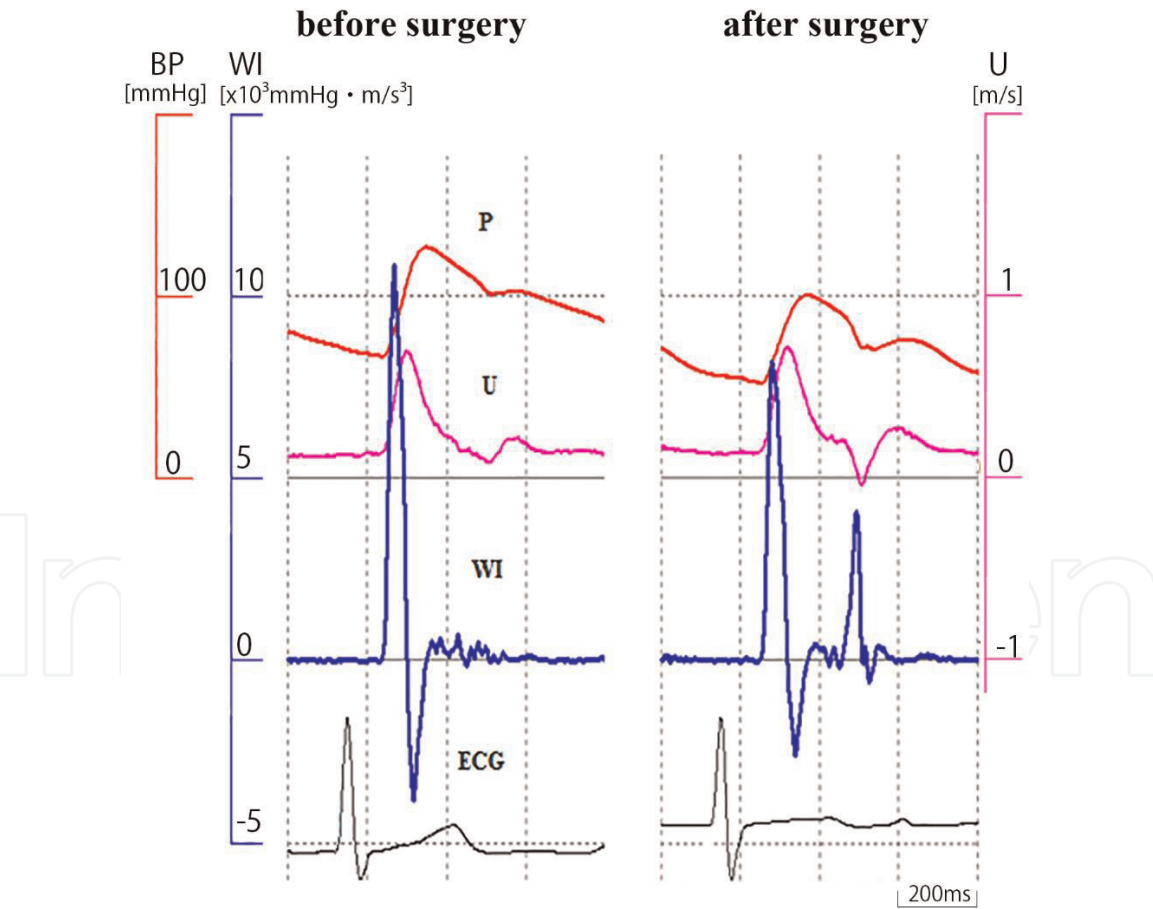


Figure 3.
Representative recordings of wave intensity in an MR subject before and after surgery. After the surgery, W_1 is decreased and W_2 is increased compared with before surgery. BP is blood pressure.

loss of arterial compliance plays an important role in LV stiffening during diastole. Indeed in our study, increase in β was associated with decrease in LVEDVI both before and after surgery (Table 3). Therefore, the diastolic LV stiffening associated with increase in β is considered to cause a decrease in W_1 in MR with higher β .

Increase in β is also associated with an increase in RegF/EOR (**Table 3**), that is, the leakage from the pressure chamber. As a result, the ventricular systolic stiffening and increase in preload by regurgitation did not work effectively in augmenting the initial pressure rise (LV peak dP/dt) in MR with higher β . Therefore, a compensatory increase in W_1 was observed only in MR with lower β and contraction preserved hearts. In other words, higher W_1 in MR is observed only in young population. On the whole in MR, W_1 was higher for lower β and lower for higher β , which made the negative slope of the regression line of W_1 on β significantly steep (**Figure 2b**). After the surgery, W_1 decreased. Though the correlation was still significant ($R^2 = 0.18$, $p = 0.0004$), the slope of the regression line of W_1 on β became gentle (**Figure 2c**), and the difference in the slope between the healthy subjects and MR groups became not significant ($p = 0.65$), which suggests that the steeper regression of W_1 on β was caused by regurgitation. There was no change in β after surgery.

5.3 Other wave intensity indices and arterial stiffness in MR patients and healthy subjects

The values of the WI indices in the MR before and after surgery and in the healthy subjects are summarized in **Table 2**. W_2 in MR was significantly reduced and negatively correlated with ERO ($r = 0.37$, $p < 0.001$). W_2 is an expansion (suction) wave produced by the heart, when blood flows out of the left ventricle into the aorta under its own momentum, which causes a rapid decline in left

	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 (RegV / total LV stroke volume); WI index (Q- W_1) is the same as **Figure 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 ^ξ $p < 0.05$, ^{ξξ} $p < 0.001$.

Table 3.
Echocardiographic data and (Q- W_1)st before and after surgery in mitral regurgitation and correlation with β [7].

ventricular pressure and a rapid increase in the maximum rate of deceleration (negative max dUf/dt) in the aorta (hence in the artery concerned) near end-ejection [5, 6, 18]. Thus, we obtained Eq. (9) above. In MR before surgery, negative max dUf/dt is very small or sometimes nearly zero as shown in **Figure 3**, left, which causes a reduction in W_2 . After the repair of regurgitation, negative max dUf/dt recovers and sometimes becomes greater than the normal values as shown in **Figure 3**, right, which causes a recovery in W_2 .

$Q-W_1$ and W_1-W_2 were temporal indices of WI, and the dependency of $Q-W_1$ and W_1-W_2 on heart rate was observed in the healthy group ($Q-W_1 = -0.51 \text{ HR} + 167$, $r = 0.44$, $p < 0.0001$; $W_1-W_2 = -1.33 \text{ HR} + 358$, $r = 0.68$, $p < 0.0001$). Therefore, based on the method by Lewis et al. [19], the standardized indices were defined as follows:

$$(Q - W_1)_{st} = 0.51 \text{ HR} + Q - W_1,$$

and

$$(W_1 - W_2)_{st} = 1.33 \text{ HR} + W_1 - W_2,$$

which were expected not to depend on HR in the healthy subjects and MR group before surgery. As compared with the healthy subjects, the MR group before surgery showed shorter $(W_1-W_2)_{st}$ (**Table 2**). The stiffness parameter β but not E_p was higher in the MR group (see Appendix A.3).

6. Clinical application of wave intensity for planning the treatment of MR

6.1 Effects of the changes in arterial stiffness on pulmonary hypertension before and after surgery

Pulmonary hypertension (PH) is one of the conclusive factors of surgical indication in MR, though the PH in MR emerges through multifactorial processes. In our study, patients with EF lower than 40% were not included. Therefore, we do not consider that the major cause of PH was left ventricular systolic failure. The results of linear univariate and following stepwise multivariate regression analyses to identify predictor variables before surgery to determine RVSP showed that ERO, β , and LAVI were independent predictor variables (**Table 4**). Increase in β , hence increase in c , increases LV afterload during initial ejection (characteristic impedance p_c [20]). In MR during ejection, there is a pressure gradient between the left ventricle and the left atrium, which is in proportion to the square of regurgitation velocity. In other words, LV pressure during ejection is paradoxically supported by regurgitation velocity toward the left atrium. Therefore, for the left ventricle to eject the blood against higher p_c , higher regurgitation velocity, hence greater regurgitation volume, is required. This makes LAVI in MR greater. In fact, the ratio of regurgitant fraction to ERO (Reg F ratio) increased with an increase in β ($r = 0.23$, $p = 0.027$) (**Table 3**). This result indicates that increased arterial stiffness exacerbates pulmonary hypertension, which will recover immediately after correction of MR (cessation of regurgitation). There was a strong correlation between RVSP and β before surgery, but this correlation disappeared after surgery (**Table 3**). The reduction rate of RVSP by surgery increased with increase in β (**Table 3**). This suggests that the surgical repair of MR caused more beneficial effect of improving PH in MR with higher β than with lower β . Surgical therapy was

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	0.44			
LVEDVI	0.15	0.145			
LVESVI	0.14	0.169			
EF	-0.02	0.853			
LAVI	0.31	0.003	0.2	0.031	1.062
E/A	0.08	0.459			
e'	-0.29	0.004	-0.17	0.114	1.62
ERO	0.36	< 0.001	0.37	< 0.001	1.039

*WI indices (W_1 , W_2 , and Q- W_1) are the same as **Figure 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 4.
Results of univariate and multivariate linear regression analyses for determinants of right ventricular systolic pressure before surgery [7].

reported to improve 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. According to Murashita et al. [21], preoperative PH disappeared after surgery in degenerative MR patients, and the most important cause of cardiovascular death after surgery was stroke, and most of patients who had recurrence of PH suffered from AF, which suggested that recurrent PH after surgery was caused by different pathophysiology due to PH before surgery.

6.2 Usefulness of wave intensity indices in predicting EF after surgery

As a surrogate for pre-ejection time, (Q- W_1)st has the potential for properly evaluating cardiac performance. Q- W_1 is the sum of PEP, the transit time of the pulse wave from the left ventricle to the carotid artery and the time from the beginning of ejection to the peak of wave 1. PEP is an old concept, but its high sensitivity and reproducibility are still useful in indicating reduced performance of the myocardium in its early stage. Therefore, the change in (Q- W_1)st also reflects the changes in myocardial properties due to remodeling. The statistical analysis using stepwise multivariate regression in our study showed that EF and (Q- W_1)st before surgery are selected predictor variables for the response variable EF after surgery (**Table 5**). (Q- W_1)st was an index with higher specificity to predict EF after surgery than the preoperative EF. The receiver-operator characteristic (ROC) curve was constructed to define optimal cut-off in (Q- W_1)st to predict low EF after surgery (<50%) using the guideline criteria outlined above. The selected cut-off value for low EF was 180 ms, which gave a sensitivity of 57% and a specificity of 87% for predicting EF after surgery lower than 50% (area under ROC 0.72, $p = 0.001$)

Variables before surgery	Univariate analysis		Multivariate analysis		
	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	−0.1	0.353			
E/A	−0.21	0.041	−0.14	0.101	1.017
e′	0.02	0.862			
RVSP	−0.1	0.338			

WI indices (W₁, W₂, and Q-W₁) are the same as **Figure 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.

Table 5.
Results of univariate and multivariate linear regression analyses for determinants of EF after surgery [7].

(**Figure 4a**). The cut-off value of EF before surgery, 60%, gave a sensitivity of 81% and a specificity of 57% for predicting reduced EF after surgery (< 50%) (area under ROC 0.73, $p = 0.001$) (**Figure 4b**). Furthermore, among the subgroup with EF before surgery < 60% ($n = 26$), the cut-off value of (Q-W₁)st, 180 ms, gave a sensitivity of 81% and a specificity of 90% for predicting reduced EF after surgery (< 50%) (area under ROC 0.73, $p < 0.001$) (**Figure 4c**).

EF before surgery is still one of the valuable parameters to predict survival rate after surgical treatment and it is expected that the best outcome is obtained when surgical treatment is taken into account before EF reduces to a level under 60% [22]. Asymptomatic stage of chronic MR patients often lasts for a long time, and such patients are usually reluctant to undergo surgery. Such situation seems to be more common in patients with lower arterial stiffness, because PH occurs less

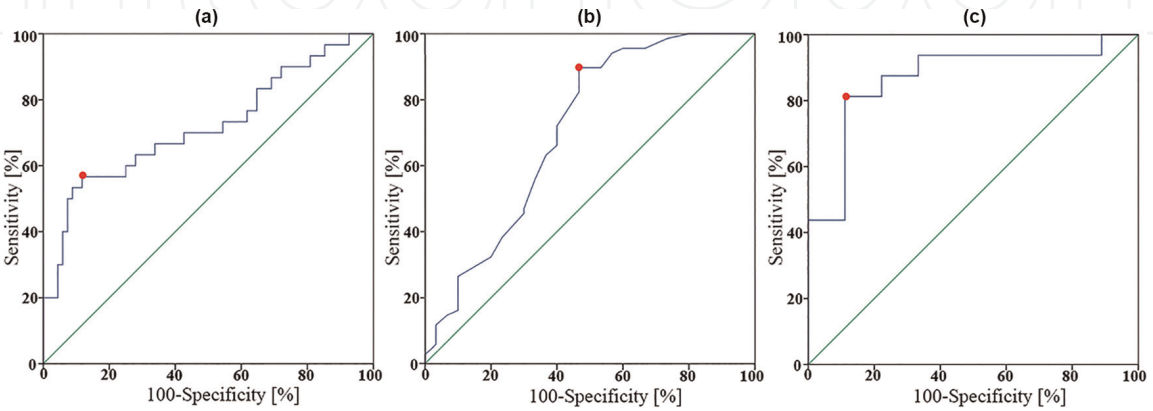


Figure 4.
Receiver-operator characteristic curves and selected combinations of sensitivity and specificity (red dots) to predict EF after surgery < 50%. (a) Cut-off value of (Q-W₁)st before surgery = 180 ms, (b) cut-off value of EF before surgery = 60%, and (c) cut-off value of (Q-W₁)st before surgery = 180 ms in the subgroup of patients with EF before surgery < 60% (from [7]).

frequently compared with subjects with higher arterial stiffness. Therefore, it is desirable to convince MR patients, who have signs of the beginning of deterioration of myocardial function, of the benefits of surgical treatment. 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.

7. Conclusions

Increased arterial stiffness affects forward flow and exacerbates pulmonary hypertension in MR. Since arterial stiffness is not reduced by vasodilator or diuretics, such medication is not so efficient at improving pulmonary hypertension caused by increased arterial stiffness, while surgical correction of MR improves the pulmonary hypertension markedly. In a paradoxical manner, pulmonary hypertension in subjects with lower arterial stiffness is caused by depressed heart, which would be difficult to recover after surgery. Prolonged $(Q-W_1)_{st}$ indicates that the heart reached a preliminary stage in remodeling that would be irreversible even after surgery.

Conflict of interest

The authors declare no conflict of interest.

A. Appendix

A.1 Echocardiographic evaluation

In this study, echocardiographic evaluation was performed in MR subjects before and after surgery using an echo machine (SONOS 7500; Philips) [23]. LV and left atrial volume (LAV) were determined using the modified Simpson's method. LAV was measured at the end-systole just before the mitral valve opening, and LV and LA volume indices, which were divided by the body surface area, were obtained. Right ventricular systolic pressure (RVSP) was obtained by adding the systolic tricuspid pressure gradient calculated by the modified Bernoulli equation and right atrial pressure [24]. Transmitral flow was assessed using pulsed Doppler by placing the sample volume at the level of leaflet tips, and early filling (E) and atrial contraction filling (A) velocities were measured. Tissue Doppler velocity of the mitral annulus in early diastole (e') was also measured. MR severity was quantified as averaged effective regurgitant orifice area (ERO) obtained by the Doppler volumetric method [25].

A.2 Statistical analysis

As for statistical analysis, comparisons among groups were performed by Student's t test or one way analyses of variance, followed by Bonferroni test when necessary. The relationships between WI indices and β were evaluated by correlation and regression analysis. Univariate regression analyses were performed for the data relating pulmonary hypertension before surgery to the variables measured before surgery and for the data relating EF after surgery to the variables measured before surgery. Then, the variables that were correlated with RVSP before surgery

and EF after surgery ($p \leq 0.1$) were entered into stepwise multivariate regression models. To obtain the threshold value of predictor variable separating a clinical diagnosis that EF after surgery $\geq 50\%$ from one that EF after surgery $< 50\%$, the ROC curves were created, and the optimal combinations of sensitivity and specificity were chosen. A p value < 0.05 was set for statistical significance.

A.3 Proper index of arterial stiffness

β is considered not to depend on pressure, while E_p decreases with a decrease in pressure. Most of the severe MR patients with hypertension were medicated with antihypertensive drugs. Therefore, in our study, systolic pressure in MR was lower than that in the healthy subject group, and there was no difference in E_p between the two groups. However, β was higher in MR. We consider that the increase in β was not caused by MR but caused by the history of hypertension. Actually, 38% of the patients were diagnosed as hypertension and medicated. Thus, β is suitable to evaluate arterial stiffness in low pressure subjects.

A.4 Use of upper arm blood pressure for calibration of carotid arterial pressure waveform

The use of upper arm pressure for calibrating carotid arterial pressure (diameter) might be criticized. In young adults, the peak pressure in the upper arm is higher than the peak pressures in central predominantly elastic arteries such as the aorta and the carotid artery (amplification). The peak pressures in central arteries increase with age due to increase in arterial stiffness by aging (late systolic peaking). In contrast, there is little or no consistent change in stiffness of the brachial or radial arteries and little change in the peak pressure in the upper arm. Therefore, the difference between central peak pressures and upper arm pressure becomes less significant in the elderly [20]. Ohte et al. [26] reported that the systematic difference between those in 82 patients (age 64.3 ± 9.4 years) remained within the practical range.

A.5 Where to set the positions for echo tracking to measure arterial diameter change waveforms

The relative change in arterial diameter, $(D_s - D_d)/D_d$, measured in an inner layer (e.g., intima) is greater than that measured in an outer layer (e.g., adventitia) due to incompressibility of the arterial wall. Therefore, β is smaller for an inner layer than for an outer layer. In some institutions, β is obtained by echo tracking the intima and in other institutions by echo tracking the adventitia. Then the obtained value of β for a patient may vary with the institution. 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 [14].

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