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Optimal timing for valve replacement in chronic aortic regurgitation: Analysis based on the myocardial contractility and postoperative prognosis

Yuzo HIROTA
Junya KUSUKAWA
Gen SHIMIZU
Kiyotaka KAKU
Yoshio KITA
Takaharu SAITO
Michihiro SUWA
Keishiro KAWAMURA

Summary

Left ventricular (LV) function was evaluated considering force-velocity and stress-shortening relationships in 14 asymptomatic (Group 1), 18 symptomatic patients (Group 2), and 53 normal subjects (Group 3) to determine the optimal time for valve replacement in patients with chronic aortic regurgitation (AR). Valve replacement was recommended for all Group 2 patients and for one patient in Group 1, who had sustained ventricular tachycardia. There was one operative death and five deaths remote from surgery; one patient in Group 1 died suddenly of undetermined cause, and four patients in Group 2 died of congestive heart failure (CHF). The LV end-systolic volume index (ESVI) was greater than 100 ml/m^2 in the five patients whose death was unrelated to surgery (remote deaths). ESVI was less than 50 ml/m^2 in all but two patients in Group 1, and more than 40 ml/m^2 in all cases in Group 2.

The index of preload, end-diastolic stress (σed), was increased in Groups 1 and 2 as compared with Group 3. A significant positive correlation was observed between end-systolic stress (σes) and ESVI ($r=0.71$, $p<0.001$) in patients with AR, and this linear line was not as steep as that of Group 3. Afterload (σes) and ejection fraction (EF) in Group 1 were within normal range, afterload was normal but EF was reduced in mildly symptomatic patients in Group 2, and severely

大阪医科大学　第三内科
高槻市大学町 2-7 (〒569)

The Third Division, Department of Internal Medicine, Osaka Medical College, 2-7 Daigakucho, Takatsuki 569

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symptomatic patients had markedly reduced EF and elevated afterload. There was a close correlation between ESVI and end-diastolic volume index (EDVI), and this was expressed as an exponential curve ($Y=21.69e^{0.006x}$, $r=0.88$, $p<0.001$). This indicates that the rate of shortening of the muscle fiber deteriorates exponentially with enlargement of the ventricle.

These observations suggest that in AR patients: 1) afterload and contractility of the ventricle remain normal in the majority of asymptomatic patients by means of compensatory hypertrophy and preload elevation (preload reserve), 2) deterioration of contractility seems to be the factor initiating CHF, and 3) progression of CHF is due to further deterioration of contractility in addition to elevation of afterload (afterload mismatch).

It is concluded that careful observations are necessary when ESVI exceeds 50 ml/m^2 in asymptomatic patients. Valve replacement is recommended when such patients develop symptoms of CHF, or either when EF falls to less than 50% or ESVI exceeds 100 ml/m^2, even if patients remain asymptomatic.

Key words
Aortic regurgitation　Valve replacement　Left ventricular function　Force-length relation　Stress-shortening relationship

Introduction

Classically, valve replacement has been recommended for patients with chronic aortic regurgitation (AR) when they develop heart related symptoms[1,2]. Although the physical activity of the majority of patients with AR is restored after surgery, some patients suffer from severe congestive heart failure (CHF) and die years after successful valve replacements[3~5]. Based on these observations, some authorities have recommended relatively early surgery, while patients remain asymptomatic[4~7]. However, relatively good operative results have been reported for patients with advanced left ventricular (LV) dysfunction[8], and Schwarz et al.[9] have reported that aortic valve replacement offers no advantage survivalwise compared to medical therapy. Some believe that valve replacement should not be performed for asymptomatic patients[10]. Whether and when we should recommend valve replacement for asymptomatic or mildly symptomatic patients is still controversial.

The purpose of this study is to clarify the optimal timing for aortic valve replacement, especially of aymptomatic and minimally symptomatic patients. Myocardial contractility was precisely evaluated according to force-length and stress-shortening relationships, and the post-operative course, as well.

Subjects and methods

The study population consisted of 32 chronic AR patients; 23 men and 9 women, all of whom consecutively underwent diagnostic cardiac catheterization from July 1977 to March 1986, and were categorized as asymptomatic (Group 1, $n=14$) or symptomatic (Group 2, $n=18$) group of CHF. Fifty-three persons who had no significant heart disease by catheterization served as controls (Group 3). These catheterizations were mainly performed to evaluate chest pain, and their coronary arteries were free of significant stenosis.

Precise descriptions of the catheterizations and data analyses have been published elsewhere[11]. LV pressure recording and cineangiography were simultaneously performed with a mikro-tip® angiocatheter (Millar Instruments) in the majority of patients. LV volumes were calculated by the area-length method of Dodge et al.[12], and expressed as corrected values divided by body surface area. Ejection fraction (EF) was calculated as: $EF=(EDV-ESV)/EDV$, where EDV = end-diastolic volume and ESV = end-systolic volume. Regurgitant fraction (RF) was obtained as: RF=(ASV-

FSV)/ASV, where ASV = angiographically determined stroke volume, and FSV = forward stroke volume as obtained by the thermodilution method in a triplicate fashion. In patients whose LV pressures were recorded with a mikro-tip® angiocatheter, LV end-diastolic (σed) and end-systolic stress (σes) were calculated as indices of preload and afterload, respectively. The thick-walled ellipsoid model of Mirsky[13] was used for evaluating stress as: $\sigma = PB/H(1 - H/B^2 - B^2/2A^2)$, where P = pressure, H = wall thickness, and A and B = long and short axes, respectively.

All data were expressed as means ± standard deviations (Mn ± SD). Unpaired Student's t test was used for statistical comparisons of data of Groups 1, 2 and 3. Linear regression was used for evaluating stress (σes)-shortening (EF) and force (σes)-length (ESVI) relations. Semilogarithmic linear regression was performed to evaluate the relationship between EDVI and ESVI. Significance of the regression line and the line of identity were determined by analysis of variance of the correlation coefficient.

Results

We recommended valve replacement for 18 symptomatic and one asymptomatic patients

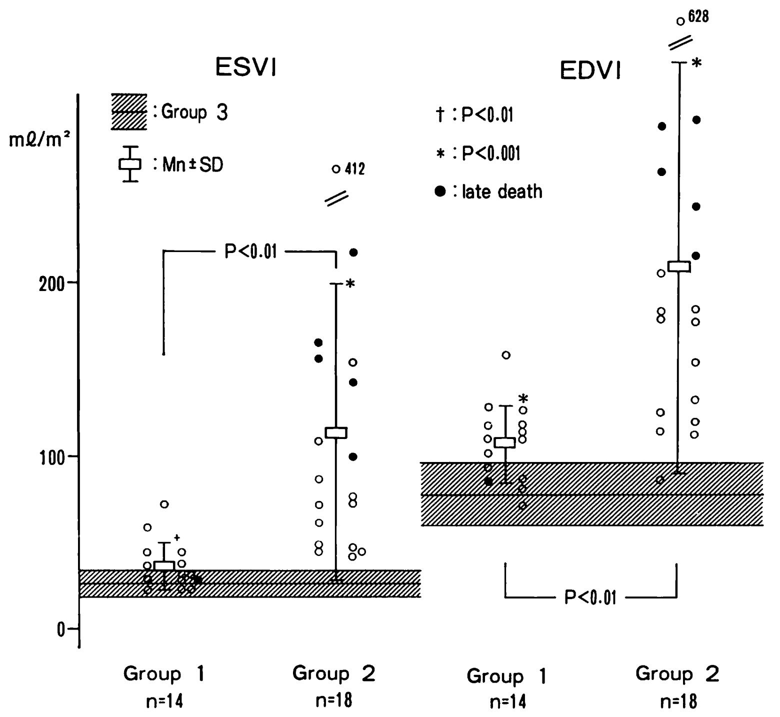

Fig. 1. Left ventricular end-systolic and end-diastolic volume indices.

The shaded areas with the bars at the middle indicate mean and one standard deviation (Mn ± SD) of the data of Group 3. Closed circles indicate patients with surgical or post-surgical death. Left ventricular (LV) end-systolic (ESVI) and end-diastolic volume indices (EDVI) are significantly increased in patients with aortic regurgitation (AR) (+ : $p<0.01$, * : $p<0.001$, compared to Group 3), and they are larger in Group 2 than in Group 1. All but two asymptomatic patients have ESVI smaller than 50 ml/m², while all symptomatic patients have ESVI greater than 40 ml/m². All patients who died of CHF had ESVI greater than 100 ml/m².

who had sustained ventricular tachycardia. Among these 19 cases, three did not consent to have the operation. All patients were followed up for one to 10 years. There was one operative death (1/16=6.2%) and there were five post-surgical deaths. Three patients who did not consent to the surgery died of CHF within five years. One who had ventricular tachycardia preoperatively died suddenly two years after the operation, and one who had good early post-operative symptomatic relief died of CHF six years later.

The angiographic characteristics of Group 1 included enlarged left ventricle (EDVI: 108±11 vs Group 3; 78±18 ml/m², $p<0.001$, ESVI: 36 ±14 vs 26±7, $p<0.01$), normal EF (0.67±0.07 vs 0.67±0.06, ns), increased preload (σed: 38± 15 vs 25±10 g/cm², $p<0.01$) and normal afterload (σes: 148±60 vs 137±56 g/cm², ns) (**Fig. 1~3**). Only two patients had ESVI greater than 50 ml/m² and EF below 0.60.

Group 2 subjects were characterized by further enlargement of the ventricle (EDVI: 211± 120 ml/m², $p<0.01$ compared with Group 1, ESVI: 114±88 ml/m², $p<0.01$) and increased preload (50±32 g/cm²). Afterload was elevated (212±69 g/cm², $p<0.001$, compared with Group 3, and $p<0.05$, compared with Group 1). RF was greater in Group 2 than in Group 1 (0.56± 0.18 vs 0.37±0.16, $p<0.01$) (**Fig. 1~3**). ESVI was greater than 40 ml/m² in all cases. Five deceased cases had ESVI greater than 100 ml/m².

The end-systolic stress-volume relationships of subjects of these three groups are shown in **Fig. 4**. It is clear that LV contractility in Group 1 is normal, except for one patient, because Groups 1 and 3 were in the same area. Although σes was normal or elevated in an individual case in Group 2, ESVI was greater than that in Group 3 in all cases. This finding suggested that contractility was depressed in Group 2.

Fig. 5 is a two-dimensional display of the stress-shortening relationship. It can be said from this analysis that contractility in subjects of Group 1 is normal or EF is maintained normal with elevated preload (preload reserve). Observing the individual data in Group 2, the level of contractility is normal in four cases, EF was reduced with normal afterload in three, and further reduction of EF was associated with the elevation of afterload in the remaining patients.

There was a good exponential correlation be-

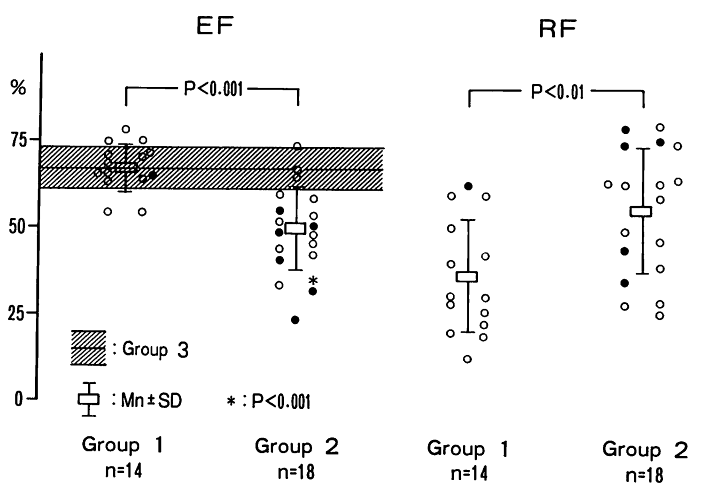

Fig. 2. Ejection fraction and regurgitant fraction.
While ejection fraction (EF) is in the normal range in Group 1, it is below normal in the majority of symptomatic cases in Group 2. Regurgitant fraction (RF) is greater in Group 2.

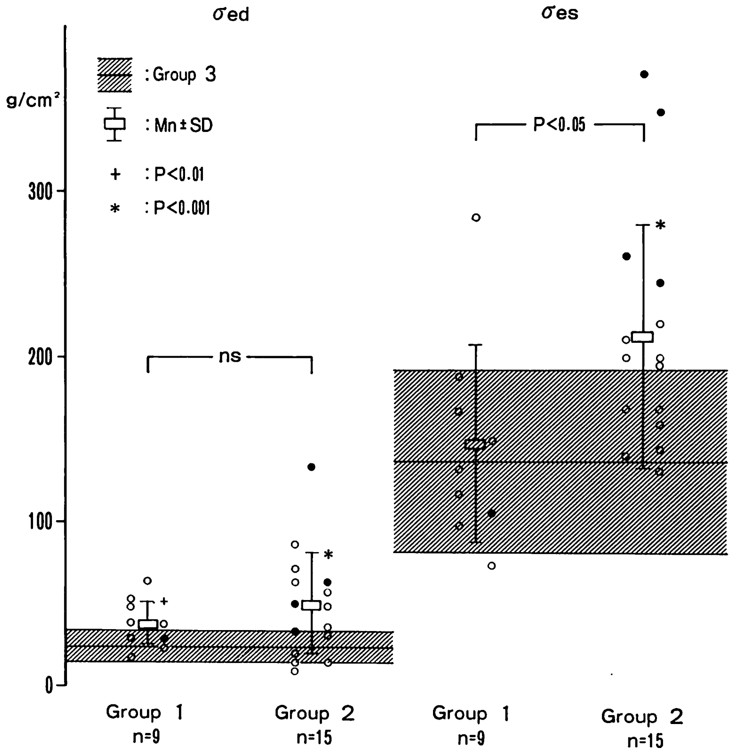

Fig. 3. The levels of preload and afterload.
The index of preload, end-diastolic stress (σed), is elevated in Groups 1 and 2 compared to those of Group 3. Afterload (end-systolic stress: σes) is in the normal range in Group 1 and is elevated in Group 2.

tween EDVI and ESVI as shown in **Fig. 6**, indicating that shortening of the left ventricle decreased as the ventricle became larger.

Discussion

It is generally accepted that the classical indication for valve replacement in patients with chronic AR is the development of cardiac symptoms. This concept is based on analyses of the natural history of this disease: relatively rapid deterioration resulting in death due to CHF is a common outcome after a lengthy asymptomatic period[1,2]. This is easily recognized when patients have overt CHF as classified in New York Heart Association Functional Class III or IV. In clinical practice, however, it is difficult to assess mild or Class II symptoms. While some patients complain of various symptoms even in the early stage mainly due to their anxiety, others deny any symptoms in the advanced stage, because they are accustomed to their disability or afraid of open heart surgery.

Although symptomatic improvement can be expected in the majority of patients following valve replacement, late analyses of cardiac function indicated incomplete recovery of LV function in some patients[14,15]. Furthermore, late CHF death was occasionally observed[3~5]. Gault and coworkers[14] reported incomplete recovery of diastolic pressure-volume relationships after successful valve replacement. To avoid such an unfavorable outcome, Henry and coworkers[4]

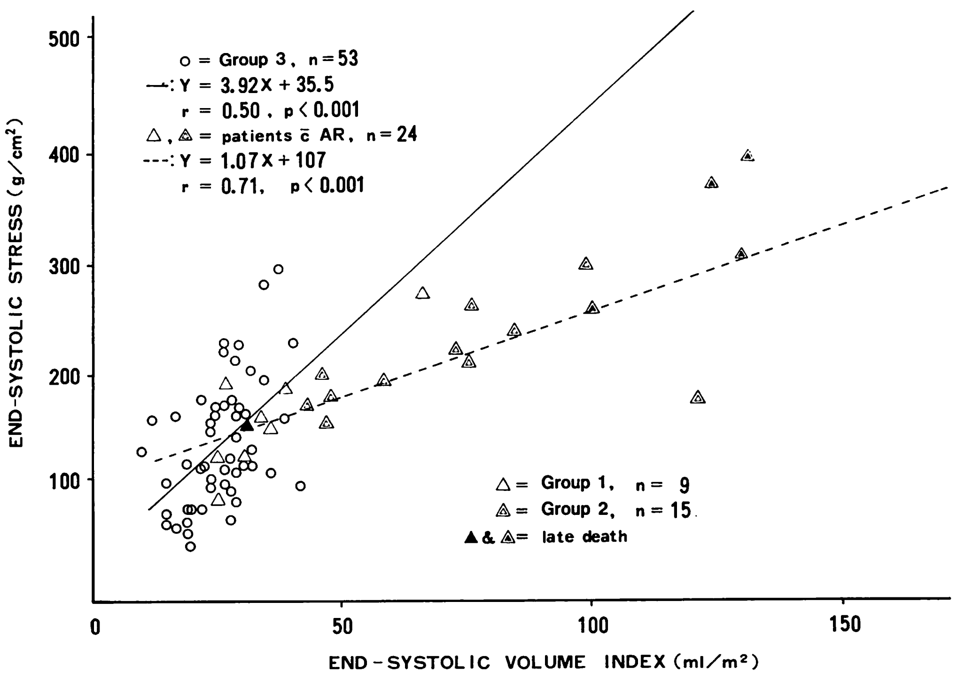

Fig. 4. Force-length relationship.

LV contractility is evaluated with the concept of force-length relationship. The σes is the external force against the contracting myocardium at end-systole. ESVI is the alternative of the muscle fiber length at end-systole. There are significant positive correlations between σes and ESVI among normal subjects and patients with AR. Both σes and ESVI are in the normal range in Group 1, while both of them are increased in Group 2. The slope of the correlation line in AR is less steep than that of normal subjects.

have recommended valve replacement in asymptomatic patients when echocardiographically measured end-systolic dimension exceeds 5.5 cm or fractional shortening becomes less than 0.25, and Gaasch et al.[15] proposed the optimal timing as the end-systolic radius-to-wall thickness (r/th) ratio to be less than 3.8 or the peak systolic stress greater than 600 mmHg/cm^2. However, Daniel et al.[16] reported that Henry's criteria, when applied clinically, were useless. Although these measurements may be obtainable noninvasively, echocardiographically-derived indices of LV function must be interpreted with a great caution, since more than 15% intra- and interobserver variations may occur when they are obtained from markedly dilated ventricles, as in AR[17]. Others have reported analyses of LV function under exercise stress, but the results are inconclusive[18~21].

The present study was undertaken to clarify the mechanisms of compensation and decompensation in chronic AR with precise analysis of LV function. It is well known that analysis of LV function considering force-length and stress-shortening relations should provide a clearer understanding of the muscle mechanics in a given disease than by comparing individual indices of cardiac function[22]. The characteristics of LV muscle mechanics in AR are : 1) The shortening rate and afterload are within the normal range, while volume overload is well compensated by the mechanisms of preload reserve

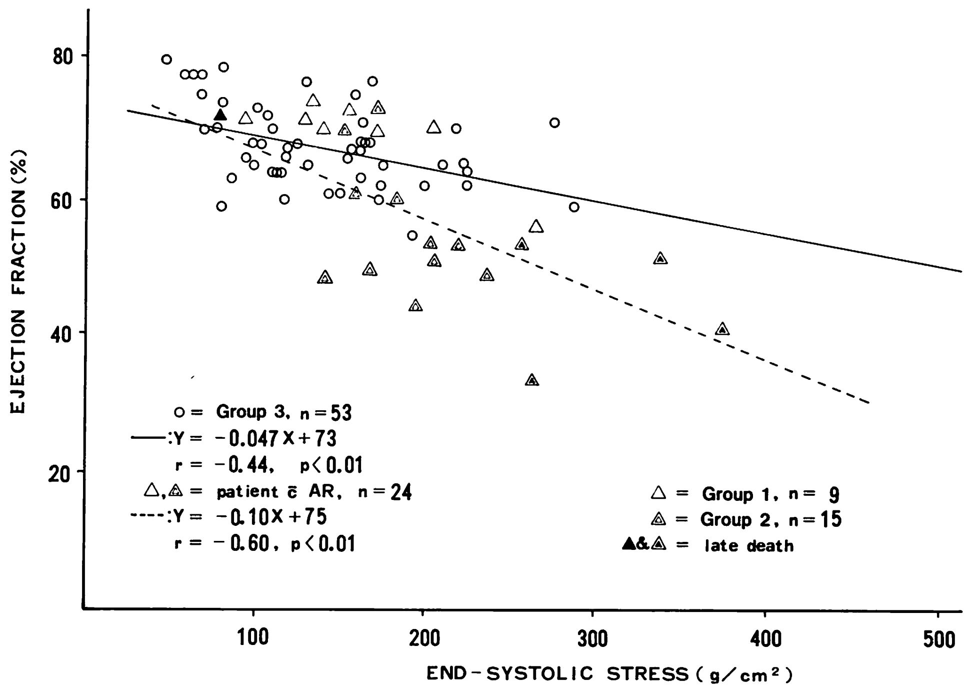

Fig. 5. Stress-shortening relationship.

EF is used as the index of myocardial fiber shortening rate, and σes as an index of afterload or the force against the contracting myocardium. While both EF and σes in Group 1 are in the normal range, EF is reduced with normal σes in mildly symptomatic patients. Patients with severe heart failure locate in the right lower side. This is due to the reduction of EF and the elevation of afterload. From this analysis, it can be said that myocardial contractility is well preserved in the majority of asymptomatic patients due to compensatory hypertrophy or by the mechanism of preload reserve, and contractility begins to deteriorate with the appearance of symptoms. The deterioration of contractility causes enlargement of LV volume and/or the elevation of afterload, but compensatory hypertrophy is inadequate at this point, and afterload mismatch causes further reduction of fiber shortening.

and compensatory hypertrophy. 2) Low EF and cardiac symptoms seem to be early manifestations of deterioration of contractility. 3) Afterload elevation is observed only in severely symptomatic patients. 4) Depressed contractility is the major determinant, with some contribution of afterload mismatch, for the development of CHF. 5) Shortening of the muscle deteriorates with enlargement of the LV cavity.

Our observations are in agreement with those of Grossman et al.[23], who reported elevated preload, and normal EF and afterload in compensated volume overload. As the left ventricle becomes enlarged, the shortening decreases exponentially, as has been reported by Abdulla et al.[24]. A markedly enlarged and poorly contracting left ventricle with elevated afterload is the most frequent finding in patients with severe CHF in any heart diseases. The majority of patients with AR and CHF have both depressed contractility due to irreversible myocardial damage and inappropriately elevated afterload (afterload mismatch) due to inadequate hypertrophy[22]. If the major cause of CHF is

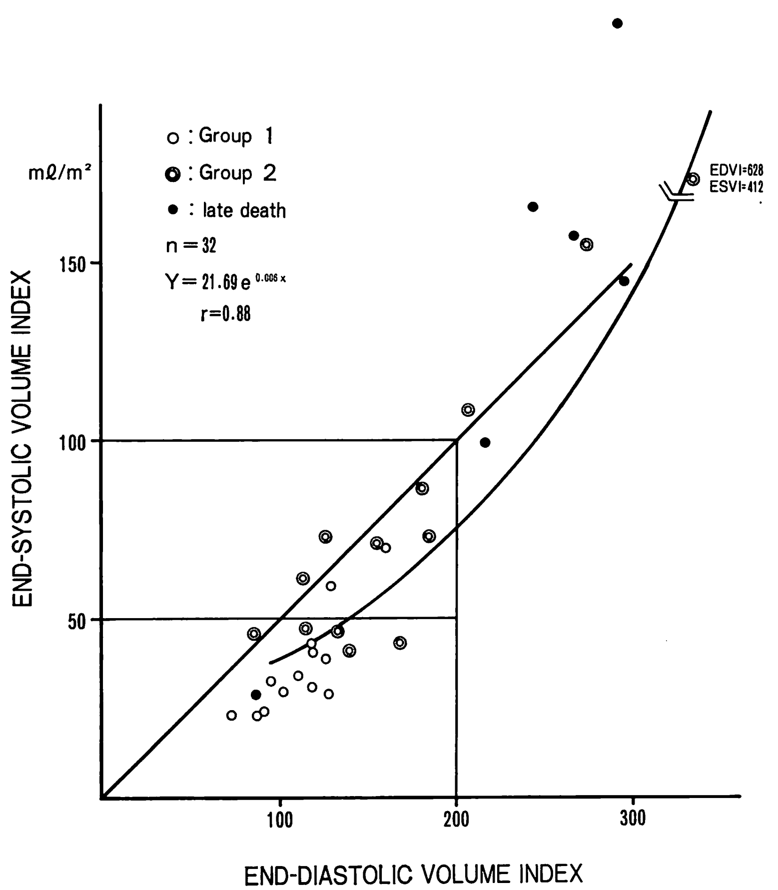

Fig. 6. Relationship between EDVI and ESVI.
The linear line in the middle indicates the ejection fraction to be 0.50. The left lower part of this line is the area in which EF is above 0.50. There is a close correlation between ESVI and EDVI, and this relation is expressed as an exponential curve with a high correlation coefficient.

irreversible myocardial damage, one cannot anticipate good prognosis after surgery. On the contrary, if afterload mismatch is the major cause, complete recovery of LV function can be anticipated after valve replacement. We cannot determine which of the two, depressed contractility or afterload mismatch, plays the major role in the development of CHF before surgery in individual patient.

Although our experience is limited, we recommend 1) careful observations of patients with AR when their ESVI exceeds 50 ml/m^2, and 2) valve replacement when they develop cardiac symptoms. We also recommend surgery when their ESVI exceeds 100 ml/m^2 or when their ejection fractions are less than 0.50. However, we should not hesitate to perform valve replacements for patients with severe CHF, since surgery can be performed with acceptable risks[8], and recovery of LV function can be expected in some patients.

要　　約

心機能特性からみた大動脈弁閉鎖不全症における弁置換術施行時期

大阪医科大学　第三内科

弘田雄三，楠川順也，清水　玄

賀来清高，北　祥男，斉藤隆晴

諏訪道博，河村慧四郎

大動脈弁閉鎖不全症 (AR) の弁置換術施行時期は，古典的には心症状の発症をもって考慮すべきであるとされてきたが，術後の経過観察などにより，早期の弁置換術を主張する意見も見られる．本研究では，AR における容量負荷に対する左室の応答機序，心不全の発現機序と弁置換術施行至適時期を検討することを目的とし，健常群 53 例のデータを AR 32 例のそれと比較，AR の心機能特性および術後経過を解析した．

結果：NYHA I 度の 1 例，II, III, IV 度の 18 例に弁置換術を勧め，3 例が拒否，1 例の手術死亡 (1/16=6.2%)，5 例の遠隔死亡を認めた．無症状群 (Group 1, n=14) では健常群 (Group 3) に比べ，左室容量 (EDV, ESV)，前負荷 (σed) は増大しているものの，駆出分画 (EF)，後負荷 (σes) は正常であり，心不全群 (Group 2, n=18) では容量はさらに増大，後負荷も増大し，EF の低下を認めた．AR では σes と ESV との間に正の直線相関関係 ($r=0.71$, $p<0.01$)，EF と σes との間に負の直線相関関係 ($r=-0.60$, $p<0.01$)，ESV と EDV との間に正の指数相関関係 ($r=0.93$, $p<0.001$) を認めた．無症状群では 2 例を除き ESVI <50 ml/m^2 であったが，心不全群では全例が ESVI>40 ml/m^2 であり，5 例の死亡例は ESVI >100 ml/m^2 であった．

考按：AR では負荷に対する代償不全，すなわち代償性肥大の終末像として心不全症状が発現する．したがって AR の手術時期決定には，症状の発現まで待たず，心機能低下の把握が重要である．具体的には ESVI が 50 ml/m^2 を越えると注意深い観察が必要であり，心不全症状の発現をもって手術適応と考えられ，無症状の症例においても，ESVI>100 ml/m^2 または EF<50% の症例では手術適応があると考えられる．

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