Late Gadolinium Enhancement Predicts Improvement in Systolic Function after Aortic Valve Replacement in Patients with Severe Aortic Stenosis

学　位　論　文

Late Gadolinium Enhancement Predicts Improvement in Systolic Function after Aortic Valve Replacement in Patients with Severe Aortic Stenosis

（ガドリニウム遅延造影は重症大動脈弁狭窄症における大動脈弁置換術後の収縮能改善の予測に有用である）

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論　文　内　容　要　旨（和文）

学位論文題名	ガドリニウム遅延造影は重症大動脈弁狭窄症における大動脈弁置換術後の収縮能改善の予測に有用である

【背景】大動脈弁狭窄症（AS）において、大動脈弁置換術（AVR）前の左室心筋線維化の進行は術後予後と関連する。近年、左室収縮能の鋭敏な指標である global longitudinal strain（GLS）と心筋線維化指標である MRI によるガドリニウム遅延造影（LGE）の関連が報告されているが、術後の左室収縮能改善の有無と術前の心筋線維化指標との関連は不明である。

【目的】LGE によって AVR 術後の左室収縮能の改善が予測可能かどうかを検討する。

【方法】対象は重症 AS のため AVR を施行した患者 29 例（中央値 73 歳、男性 52%）であった。重症大動脈弁閉鎖不全症合併、中等度以上の僧帽弁閉鎖不全症合併、心筋梗塞の既往や狭心症合併、心房細動合併、左脚ブロック、透析症例は除外とした。術前に 2D speckle tracking 法による GLS と、MRI 画像から LGEcore (g, > 5 SD)、LGEgray (g, 2 SD- 5 SD)、LGEcore+gray を評価した。13 例では術中左室心筋生検標本から fibrous index (FI, %)を算出した。上記各指標の関連を検討し、また術後 1 年における、術後の GLS 改善の予測因子を検討した。

【結果】GLS は FI（$r = 0.68$, $p < 0.05$）、LGEcore （$r = 0.38$, $p < 0.05$）LGEgray（$r = 0.57$, $p < 0.01$）、LGEcore+gray（$r = 0.60$, $p < 0.01$）と有意に相関し、FI は LGEcore（$r = 0.62$, $p < 0.05$）、LGEcore+gray（$r = 0.61$, $p < 0.05$）と相関した。GLS は術前に比べ術後 1 年で有意に改善し（GLS_{pre} to $GLS_{post1year}$; -16.9 to -19.9%, $p<0.01$）、GLS 改善群（GLS ≥ -19.9%, n = 14）では非改善群(n = 12)に比べ術前の LGEcore が有意に低値であった（改善群 vs. 非改善群; 1.34 vs. 4.70 g, $p < 0.01$）。多変量解析では LGEcore が術後収縮能改善の予測因子であった（$\beta = 0.446$, $p < 0.05$）。ROC 解析により術後の GLS 改善を予測する LGEcore の cut-off 値は 2.86 g（AUC 0.81, 感度 78.6%, 特異度 83.3%)であった。

【結語】重度 AS 患者において、LGEcore が AVR 術後の左室収縮能改善を予測する因子として有用である。

論文概要

大動脈弁狭窄症（aortic stenosis: AS)患者において、持続的な左室心筋への圧負荷により心筋線維化が惹起される。この左室心筋線維化が左室収縮能低下を引き起こし、予後不良因子とされている。これまで、病初期に左室心筋に生じる diffuse fibrosis は可逆性であるが、病期の進行に伴い focal fibrosis が出現し、不可逆性となることが報告されている。

重症 AS に対しては、大動脈弁置換術（aortic valve replacement: AVR)が施行されるが、術後圧負荷が解除されたにも関わらず左室収縮能低下が進行し、心不全が出現・進行する症例が存在する。しかしながら、術後左室収縮不全進行の予測は未だ困難であり、適切な手術時期の見極めには左室心筋の線維化の評価を行い、AVR 後に左室収縮能改善の予測因子となるかどうかを検討する必要がある。

これまで、左室心筋線維化の評価法として心筋生検が用いられてきたが、侵襲性が高く、日常臨床において用いるのは困難である。近年、心臓 MRI 検査によるガドリニウム遅延造影検査（LGE）による心筋線維化の定量評価が行われるようになり、LGE による大動脈弁置換術後の予後に関する報告がなされている。一方、心エコー図法による左室収縮能の鋭敏な指標である global longitudinal strain (GLS)は、左室駆出率（LVEF)の低下のない AS 患者においても低下し、予後と関連することが報告されている。しかしながら、LGE 指標を用いて、AVR 後の GLS 改善を予測可能か否かは明らかでない。

今回我々は、AVR 後の GLS を指標とした左室収縮能の改善が LGE によって予測可能か否かを明らかにすることを目的として研究を行った。

対象は AVR を予定された重症 AS 患者 29 人（平均年齢 73 歳、男性 52%）であった。術前に心エコー図検査による GLS、および MRI 検査による LGE を算出した。LGE は正常心筋を基準点とし、LGEcore (> 5 SD +基準点, focal fibrosis の指標)、LGEgray (2 SD- 5 SD +基準点，diffuse fibrosis の指標)および LGEcore+gray を評価した。同意の得られた 13 例においては、術中左室心筋生検を行い、病理組織学的検討により、心筋組織に占める割合を線維化面積（fibrosis index: FI %)として算出した。上記より、GLS、LGE、FI の関係を検討した。さらに、術後 1 年に再度心エコー図検査を行い、術後 GLS の改善を LGE により予測できるかについて検討した。

全症例において、GLS は LGEcore ($r = 0.38$, $p < 0.05$)、LGEgray ($r = 0.57$, $p < 0.01$)、LGEcore+gray ($r = 0.60$, $p < 0.01$)と相関関係を認めた。また、FI は LGEcore($r = 0.62$, $p < 0.05$)、LGEcore+gray ($r = 0.61$, $p < 0.05$)、GLS ($r = 0.68$, $p < 0.05$)と相関関係を認めた。

術後 1 年において GLS は有意に改善した（術前 to 術後 : -16.9% to -19.9%, $p<0.05$)。術後 GLS の中央値を用いて全症例を改善群（術後 GLS ≥ -19.9%)および非改善群(術後 GLS < -19.9%)の 2 群に分け、GLS 改善の予測因子の検討を行った。2 群間に

おいて、術前 GLS およびその他の心エコー図指標に差は認められなかったが、LGEcore は改善群で非改善群に比べ有意に小さかった。(改善群 vs 非改善群: 1.34 g vs 4.70 g, $p < 0.01$)。多変量解析により、LGEcore は術後 GLS 改善を予測しうる独立した規定因子であり($r = 0.446$, $p < 0.05$)、LGEcore のカットオフ値は 2.86 g（感度 78.6%、特異度 83.3%）であった。

本研究の結果から、重症 AS 患者における AVR 後の左室収縮能の改善（GLS 改善）を LGE を用いて予測可能か否か検討し、以下の知見を得た。1）術前 GLS、LGE および FI に有意な相関関係を認めた。2）LGEcore は術後 1 年の GLS 改善を予測する独立した規定因子であった。3）LGEcore 2.86 g をカットオフ値として、術後 GLS 改善を予測可能であった。

無症状の重症 AS 患者に対する手術適応は LVEF 50%未満が推奨されているが、LVEF が低下する前から GLS は低下し、左室心筋線維化は進行している。本研究の結果から、LGEcore は AVR 後の収縮能改善の有用な予測因子であり、LVEF が保たれている重症 AS 患者における至適手術時期の決定の一助になると考えられた。

ABSTRACT

BACKGROUND Myocardial fibrosis, as detected by late gadolinium enhancement (LGE) magnetic resonance imaging (MRI), is related to mortality after aortic valve replacement (AVR) in patients with severe aortic stenosis (AS). However, whether LGE predicts improvement in LV systolic function after AVR remains unclear.

OBJECTIVES This study aimed to determine whether myocardial fibrosis quantified by LGE MRI predicts improvement in left ventricular (LV) systolic function after AVR in patients with severe AS.

METHODS Twenty-nine patients with severe AS who were scheduled to undergo AVR were enrolled in this study. Two-dimensional echocardiography and contrast-enhanced MRI were performed before AVR. Global longitudinal strain (GLS) as an index of LV systolic function and LGEcore (g: > 5 SD of normal area), LGEgray (g: 2 SD- 5 SD), and LGEcore+gray (g) were measured. The fibrosis index (FI, %) was assessed using intraoperative LV myocardial specimens obtained from 13 patients. One year after AVR, changes in GLS were examined by echocardiography to assess improvement in LV function.

RESULTS GLS correlated with LGEcore ($r = 0.38$, $p<0.05$), LGEgray ($r = 0.57$, $p < 0.01$) and LGEcore+gray ($r = 0.60$, $p < 0.01$), and FI correlated with LGEcore ($r = 0.62$, $p < 0.05$), LGEcore+gray ($r = 0.61$, $p < 0.05$), and GLS ($r = 0.68$, $p < 0.05$), preoperatively. GLS was significantly improved at one year after AVR ($GLS_{baseline}$ to GLS_{1year}: -16.9% to -19.9%, $p < 0.05$). LGEcore was significantly lower in patients with improved GLS ($GLS_{1year} \geq$-19.9%) compared to those with no improved GLS (1.34 g vs. 4.70 g, $p < 0.01$). Multivariate analysis revealed that LGEcore independently predicts improvement in GLS after AVR ($r = 0.446$, $p < 0.05$), with a cut-off value of 2.86 g (AUC 0.81; 78.6% sensitivity and 83.3% specificity).

CONCLUSION LGE predicts improvement in LV systolic function after AVR in patients with severe AS.

KEYWORDS: Aortic stenosis; myocardial fibrosis; global longitudinal strain; late gadolinium enhancement; aortic valve replacement

ABBREVIATIONS

AS = aortic stenosis

AUC = area under the curve

AVR = aortic valve replacement

BNP = brain natriuretic protein

CKD = chronic kidney disease

ECV = extracellular volume

EF = ejection fraction

FI = fibrosis index

GLS = global longitudinal strain

IQR = interquartile ratio

LAVI= left atrial volume index

LGE = late gadolinium enhancement

LV = left ventricle

MPG = mean pressure gradient

MRI = magnetic resonance imaging

SAP = systolic arterial pressure

SD = standard deviation

SVi = stroke volume index

Zva = valvulo-arterial impedance

INTRODUCTION

Aortic stenosis (AS) remains a diagnostic and therapeutic challenge especially in elderly patients. Left ventricular (LV) myocardial fibrosis is associated with progression of LV hypertrophy, which compensates for pressure overload in patients with AS. Myocardial fibrosis is classified as focal fibrosis or diffuse fibrosis, with the latter being an early phenomenon preceding the former (1). LV myocardial advanced fibrosis, especially focal fibrosis or scars, reportedly correlates with LV systolic dysfunction, and the severity of fibrosis is known to be associated with a poor late prognosis (2). In some cases, LV dysfunction and heart failure further progress after aortic valve replacement (AVR). Therefore, the optimal timing for AVR needs to be determined while considering the grade of LV myocardial fibrosis. While myocardial biopsy is the gold standard for detecting myocardial fibrosis, its general applicability is limited due to the invasiveness of the procedure.

Cardiac magnetic resonance imaging (MRI) is widely used for assessment of myocardial fibrosis (1). Late gadolinium enhancement (LGE) MRI is a useful method for detecting myocardial fibrosis. Myocardial fibrosis detected by LGE has been reported to correlate with late mortality in patients with AS after AVR (3).

Several studies have reported that global longitudinal strain (GLS), an index of LV systolic function assessed by echocardiography, is reduced even in AS patients with preserved LV ejection fraction (EF) (4). Impaired GLS is known to correlate with AS severity, increased left ventricular mass index (LVMI) (5), and all-cause mortality in patients with AS (6). However, few studies have examined which preoperative examinations predict improvement in GLS after AVR.

This study aimed to examine whether LGE MRI predicts improvement in GLS after AVR in patients with severe AS.

METHODS

STUDY DESIGN AND PATIENT RECRUITMENT. This prospective observational study was conducted in 29 patients with severe AS who underwent AVR according to AHA/ACC

Guideline (7) from January 2014 to July 2017. Severe AS was defined as an aortic valve area <1.0 cm^2, peak aortic valve velocity >4.0 m/s, and mean pressure gradient >40 mmHg (8). Exclusion criteria were patients with concomitant severe aortic regurgitation, moderate to severe mitral regurgitation, and a previous history of ischemic heart disease, atrial fibrillation, left bundle branch block (possibility of complete atrioventricular block by biopsy), or chronic kidney disease (CKD: eGFR <30 ml/min/1.73 m^2 is a contraindication to gadolinium enhanced-MRI) (9).

All patients underwent echocardiography and MRI prior to AVR. Myocardial biopsy specimens were collected intraoperatively from 13 patients who provided informed consent. We evaluated relationships among the parameters of echocardiography and MRI and myocardial specimens. Echocardiography was also performed one year after AVR to assess the correlation between preoperative LGE and postoperative GLS improvement.

This study was approved by the institutional review board of Fukushima Medical University and was conducted in compliance with the principles of the Declaration of Helsinki. All patients provided written informed consent.

ECHOCARDIOGRAPHY. We performed transthoracic echocardiography to assess aortic valve function and LV systolic and diastolic function using the Acuson SC2000^{TM} system (SIEMENS: Mountain View, CA, USA) with a 4-MHz transducer (10, 11). Echocardiographic parameters included LV wall thickness and dimension, LV volume and LVEF, left atrium volume index (LAVI), E/A, e', E/e', and AS indices [aortic valve area, peak velocity, mean pressure gradient (MPG), and valvulo-arterial impedance (Zva)]. Zva was defined as the ratio of estimated LV systolic pressure (the sum of systolic arterial pressure (SAP) and MPG) to stroke volume index (SVi): Zva = (SAP+MPG)/SVi (12). LV mass index was calculated by the cube formula in the parasternal long-axis view (10).

2D-GLS was examined by 2D speckle tracking echocardiography using the SC2000 workplace system VVI^{TM} (SIEMENS: Mountain View, CA, USA). We assessed endocardial GLS as the average of GLSs in apical 2-, 3-, and 4-chamber views (Figure 1) (13).

CARDIAC MRI. Cardiac MRI was performed on a 1.5-T scanner (Vantage Titan™: Canon Medical Systems, Otawara, Japan) according to the standard LGE protocol (14). Ten minutes before image acquisition, 1.0 M gadobutrol (Gadovist™: Bayer, Berlin, Germany), a gadolinium-based contrast agent, was administered systemically to patients with eGFR ≥30 ml/min/1.73 m^2.

Cardiac MRI was analyzed using a post-processing workstation (Ziostation2™: Ziosoft, Tokyo, Japan). The contours of the LV endocardium and epicardium were traced semi-automatically in short-axis slices. The region of interest (ROI) was selected within the remote reference myocardium to set the standard deviation (SD) (15). We evaluated LGEs as parameters of fibrosis, calculated on the workstation as areas with the above-threshold signal intensity compared to the remote reference myocardium in the ROI (LGEcore: >5 SD; LGEgray: 2 SD- 5 SD; LGEcore+gray: LGEcore plus LGEgray) (Figure 2) (16, 17).

INTRAOPERATIVE BIOPSY. Intraoperative myocardial biopsy specimens were taken from 13 of the 29 patients. Myocardial specimens roughly 8 mm^3 in volume were harvested from the ventricular septum following aortic valve resection. All specimens were preserved in 20% formalin, embedded in paraffin, cut into 5-μm-thick sections, and stained with Elastica-Masson stain. The myocardial muscle and fibrous tissue was observed at a magnification of 100x (18). The fibrosis index (FI) was defined as the ratio (in percentage) of fibrosis tissue to the total myocardial field using Image J (19). For each patient, FI was quantified in five different fields representative of all myocardial samples (Figure 3).

RELATIONSHIPS AMONG ECHOCARDIOGRAPHY, MRI, AND MYOCARDIAL SPECIMENS AT BASELINE AND FOLLOW-UP. We evaluated relationships among preoperative GLS by echocardiography, LGEcore, LGEgray, and LGEcore+gray by MRI, and FI derived from myocardial specimens.

Patients underwent echocardiography one year after AVR and were divided into the following two groups according to GLS improvement: the improvement group (postoperative GLS greater than or equal to median) and the non-improvement group (post-operative GLS less than median).

Pre- and postoperative echocardiographic parameters and LGEs were compared between the improvement group and the non-improvement group in order to assess whether it is possible to predict improvement in GLS after AVR. Moreover, multivariate analysis was performed to determine which parameters are independent predictors of GLS improvement.

STATISTICAL ANALYSIS. The planned sample size for this study was based on the ability to detect a 3% decreasing of GLS after AVR compared with the preoperative GLS. To account for the possibility of patients loss of follow-up and to ensure a real clinical difference, the planned sample size was 30 patients. Statistical analyses were performed using SPSS™ software version 23 (IBM, Armonk, New York). Categorical variables were expressed as percentages. All continuous variables were expressed as a median (interquartile range: IQR). Comparisons between the two groups were assessed by the Mann-Whitney U test for non-normally distributed variables and the chi-square test for categorical variables. Log transformation was used to normalize the distribution of preoperative GLS, LGEcore, and LGEcore+gray. Multiple linear regression was used to predict postoperative improvement in GLS based on preoperative GLS, LGEcore, and LGEcore+gray. For each parameter, log-converted values were used for multivariate analysis (i.e., x: [log x]/ [SD of log x]).

RESULTS

BASELINE CHARACTERISTICS. Table 1 summarized preoperative baseline characteristics of the 29 patients (age, 73 [IQR: 66 – 78] years; 52% male) included in this study. Nine patients presented with symptoms of heart failure (New York Heart Association functional class II in 8 patients and III in 1 patient), and 16 patients presented with symptoms of AS (dyspnea: 9, chest pain: 4, syncope: 3). In this cohort, patients had several

atherosclerotic risk factors (hypertension, diabetes mellitus, hyperlipidemia, and/or current smoking). Brain natriuretic peptide was 85.0 pg/ml (IQR: 39.1-183.0).

PREOPERATIVE ECHOCARDIOGRAPHIC AND MRI FINDINGS. Table 2 shows echocardiographic parameters at baseline. All patients had high-gradient severe AS, with a peak velocity of 4.72 m/s (IQR: 4.30 – 5.25), mean pressure gradient of 51.0 mmHg (41.4 – 68.1), aortic valve area of 0.67 cm^2 (0.57 – 0.79), and Zva of 5.40 mmHg/ml/m^2 (4.53 – 6.5). LVEF was well-preserved at 65.7% (61.9 – 68.5), while GLS was reduced at -16.5% (-18.2 – -14.2). LV hypertrophy was observed (LVMI: 123.2 g/m^2), but no severe diastolic dysfunction with increased LA pressure was noted (E/A: 0.63 and E/e': 12.4).

The parameters of myocardial fibrosis by MRI were as follows: LGEcore 3.0 (IQR: 1.2 – 6.7) g, LGEgray 10.8 (7.3 – 17.8) g, and LGEcore+gray 15.0 (9.5 – 22.7) g, and these showed no severe myocardial fibrosis. As shown in Figure 4, significant correlations were observed between GLS and LGEcore ($r = 0.38$, $p < 0.05$), LGEgray ($r = 0.57$, $p < 0.01$) and LGEcore+gray ($r = 0.60$, $p < 0.01$).

RELATIONSHIPS BETWEEN MYOCARDIAL FIBROSIS AND IMAGING PARAMETERS. The FI obtained from myocardial biopsy specimens of 13 patients was 5.3% (IQR: 2.8 – 16.0). FI correlated with LGEcore ($r = 0.62$, $p < 0.05$) and LGEcore+gray ($r = 0.61$, $p < 0.05$), but not LGEgray (Figure 5). FI strongly correlated with GLS ($r = 0.68$, $p < 0.05$) (Figure 6).

FOLLOW-UP ECHOCARDIOGRAPHY AFTER AVR. There was no all-cause death or hospitalization due to heart failure at one year after AVR. We examined echocardiography in 26 patients; reasons for not performing follow-up echocardiography included patient refusal, cost of echocardiography, and other socioeconomical reasons. The results of comparisons of echocardiographic parameters before and after AVR are summarized in Table 3. After AVR, aortic valve function was significantly improved in terms of peak velocity (4.73 to 2.55 m/s),

mean pressure gradient (50.5 to 14.1 mmHg), aortic valve area (0.65 to 1.47 cm^2), and Zva (5.46 to 4.48 mmHg/ml/m^2). Regression of LV hypertrophy was observed [interventricular septum thickness, 13.1 to 10.8 mm ($p < 0.001$); posterior wall thickness, 13.0 to 10.1 mm ($p < 0.001$); LVMI, 123.2 to 92.9 g/m^2 ($p < 0.001$)], with improved diastolic function [E/A, 0.62 to 0.91 ($p < 0.05$); e', 5.2 to 7.5 cm/sec ($p = 0.001$)]. A significant improvement in GLS was also observed after AVR (-16.9% to -19.9%).

PREDICTION OF GLS IMPROVEMENT AFTER AVR. We divided the 26 patients who underwent follow-up echocardiography according to median postoperative GLS: the improvement group (≥ -19.9%; n = 14) and the non-improvement group (< -19.9%; n = 12). The comparisons of patient characteristics, echocardiographic parameters, and MRI parameters between the two groups are shown in Table 4.

No significant differences were observed in age, implanted valve size, and blood pressure between the improvement and non-improvement groups. Preoperative echocardiographic parameters did not differ between the two groups. Postoperatively, however, significant improvements were observed in LV hypertrophy (IVS and PW) and LV diastolic function (LVMI and e′) in the improvement group compared to the non-improvement group.

LGEcore and LGEcore+gray were lower in the improvement group compared to the non-improvement group. LGEgray did not differ between the two groups.

In the univariate analysis, LGEcore and LGEcore+gray were significant predictors of GLS improvement after AVR (LGEcore: $\beta = 0.446$, $p = 0.011$; LGEcore+gray: $\beta = 0.319$, $p = 0.056$) (Table 5). On the other hand, no preoperative echocardiographic parameters including GLS predicted improvement in GLS. In the multivariate analysis, LGEcore was found to be an independent predictor of postoperative improvement in GLS ($\beta = 0.446$, $p = 0.022$) (Table 5).

In the ROC analysis, the area under the curve was 0.81 for predicting postoperative GLS improvement (≥ -19.9%) by LGEcore, with a cut-off value of 2.86 g (sensitivity, 78.6%; specificity, 83.3%) (Figure 7A).

Figure 7B shows changes in GLS before and after AVR for each patient. Patients with low LGEcore (< 2.86 g) showed improved GLS after AVR compared to those with high LGEcore (≥ 2.86 g).

DISCUSSION

In this study, we investigated whether preoperative LGEs could predict improvement in GLS after AVR in patients with preserved LVEF and reduced GLS. The major findings are as follows: 1) Preoperative examinations revealed significant correlations among GLS, LGEs, and FI; 2) One year after AVR, GLS was improved in a manner dependent on preoperative LGEcore; and 3) LGEcore can predict postoperative improvement in GLS with a cut-off value of 2.86 g. These findings suggest that myocardial fibrosis as detected by LGE predicts improvement in GLS after AVR, and that LGE can help determine the optimal timing for AVR in patients with severe AS.

Microscopic changes in LV are characterized by cardiomyocyte hypertrophy and extracellular matrix expansion in patients with AS. These conditions are caused by either focal replacement fibrosis (scar) or reactive and interstitial diffuse fibrosis (2, 3, 20-24). A recent prospective observational cohort study reported that focal fibrosis (scars) as detected by LGE does not resolve, while diffuse fibrosis and myocardial hypertrophy as assessed by extracellular volume (ECV) show significant regression after AVR in patients with symptomatic severe AS (20). It remains unclear as to which type of LV myocardial fibrosis (i.e., focal or diffuse) plays an important role in persistent systolic dysfunction after AVR.

Several recent studies used LGE cardiac MRI for quantification of LV myocardial fibrosis with signal thresholding techniques (25). While the 2 SD threshold method is often used to detect myocardial fibrosis, different thresholds (3 SD, 5 SD, and 7 SD) have been proposed for detecting hypertrophic cardiomyopathy and acute/chronic myocardial infarction,

with different mean LGE volumes (26). The thresholds of 3 SD and 2-3 SD are used for the core infarct zone and the gray infarct zone, respectively, to assess myocardial fibrosis in patients with ischemic heart disease (27). The gray infarct zone has been reported to be a predictor of mortality (27) in post-myocardial infarction and ventricular arrhythmia (16, 17). Azevedo et al. reported that LGE (> 2 SD) could predict all-cause mortality in patients with severe AS (2), and Lee et al. reported that LGE (> 5 SD) was a predictor of poor prognosis in patients with AS (1). Yet, no study has examined which threshold (i.e., 2 SD or 5 SD) better predicts improvement in contractile function after AVR. Therefore, different optimal thresholds are used to predict specific heart disease outcomes. In the present study, we used a threshold of 2- 5 SD for LGEgray and >5 SD for LGEcore in order to predict both GLS reduction before AVR and GLS improvement after AVR.

According to previous studies, LGEcore and LGEgray reflect focal fibrosis and diffuse mild interstitial fibrosis, respectively (16). Reverse remodeling after AVR has been shown to be primarily due to regression of diffuse fibrosis accompanied by myocardial cell hypertrophy (20). In the present study, LGEcore, but not LGEgray or LGEcore+gray, was found to be a predictor of GLS improvement after AVR. While LGEgray (i.e., mild interstitial fibrosis) can be reversible, LGEcore (i.e., focal fibrosis) is unlikely to improve after AVR. Thus, our findings suggest that the degree of focal fibrosis before AVR is a determining factor for GLS improvement after AVR in patients with severe AS.

In addition, there was no significant difference in LGEgray between the group of improved GLS and the group of no improved GLS. In this study, FI was determined by pathological analysis using Elastica-Masson staining, and therefore, indicated fibrosis and fibrillary collagen but not interstitial fluid. In contrast, LGEgray reflects interstitial fluid as well as extracellular matrix. This difference may explain why LGEgray was not correlated with FI. LGEgray could not predict improvement of LV systolic function possibly because it reflects reversible components after AVR.

GLS is reduced in symptomatic patients with severe AS, and a decrease in GLS is a predictor of all-cause mortality (6). GLS is also a predictor of future major adverse cardiac

events in asymptomatic patients with severe AS and preserved LVEF (28). Thus, assessing GLS is clinically important in patients with potential systolic dysfunction and preserved LVEF. Lee et al. reported that native T1 values by cardiac MRI as an index of diffuse interstitial fibrosis correlated with GLS (29). In a previous study, histological findings suggested improved GLS in patients with mild fibrosis, but not in those with moderate or severe fibrosis, nine months after AVR (22). It remains unclear as to whether a decrease in GLS correlates with values of focal fibrosis and/or diffuse mild fibrosis, and whether LGEcore (i.e., focal fibrosis) and LGEgray (i.e., diffuse mild fibrosis) are predictors of GLS improvement after AVR.

GLS reduction also correlates with several factors such as myocardial fibrosis (30), pressure overload, and obesity (31). Dihn et al. reported that enlarged LVMI is reflected in abnormalities of GLS in patients with AS (5). The main cause of GLS impairment is still unknown, as well as the prospect for GLS improvement after AVR. In the present cohort study, patients had preserved LVEF with a slight decrease in GLS, and myocardial specimens showed mild fibrosis compared to severity of fibrosis in the previous reports (1, 29). However, given that not all patients showed improved GLS after AVR, predictors of GLS improvement after AVR need to be investigated further.

To the best of our knowledge, this is the first study to evaluate whether LGE as an index of focal fibrosis and/or diffuse fibrosis could predict improvement in GLS one year after AVR. Preoperative GLS strongly correlated with LGEgray, but weakly correlated with LGEcore. On the other hand, LGEcore was found to be a predictor of GLS improvement after AVR. The use of different thresholds, i.e., >5SD for LGEcore and 2-5SD for LGEgray, allowed us to detect potential systolic dysfunction with preserved LVEF (LGEgray), and to predict improvement in GLS (LGEcore) after AVR.

Recent therapeutic strategies for asymptomatic severe AS include AVR, which is recommended only when LVEF is less than 50% (7). However, severe AS patients with preserved LVEF already has LV myocardial fibrosis (32). In patients with extensive focal fibrosis, myocardial damage persists even if LV afterload is decreased by AVR. Thus,

myocardial fibrosis needs to be evaluated noninvasively in order to predict prognosis after AVR in a clinical setting. Since focal fibrosis as detected by LGEcore (<2.86 g) is an independent predictor of GLS improvement after AVR, surgical therapy should be considered before patients develop irreversible LV dysfunction.

STUDY LIMITATIONS. This study has several limitations. First, this study was conducted at a single center with a small number of participants. Therefore, our findings need to be confirmed in a larger cohort. Second, we excluded patients with CKD because of a contraindication to contrast-enhanced MRI. Thus, the results of the present study may not apply to patients with CKD, which is a common disorder in elderly patients. Other methods to assess LV myocardial fibrosis, e.g., ECV by MRI (33, 34), should be considered. Third, we assessed GLS by 2D echocardiography, not 3D echocardiography. A significant correlation has been reported between 2D GLS and 3D GLS in patients with AS, and 3D GLS as well as 2D GLS are reportedly predictors of major adverse cardiac events (28).

CONCLUSIONS

This prospective observational study demonstrated that improvement in systolic function after AVR can be predicted in patients with severe AS. Preoperative LGEcore is the most effective predictor of contractility improvement after AVR in patients with severe AS and preserved LVEF, and could help determine the timing of AVR.

ACKNOWLEDGEMENTS

We thank Dr. Tetsuya Ohira, Professor of Department of Epidemiology, Fukushima Medical University, for his advice on statistical analysis.

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FIGURE LEGENDS

Figure 1. Measurement of GLS by 2D Echocardiography

Endocardial GLS was examined by 2D speckle tracking echocardiography using the SC2000 workplace system VVI^{TM}. GLS as the average of GLSs in apical 2-, 3-, and 4-chamber views was assessed using the same procedure.

GLS: global longitudinal strain

Figure 2. Measurement of LGE by MRI

LGEcore, LGEgray, and LGEcore+gray were calculated as areas with the above-threshold signal intensity in the ROI (≥5SD for LGEcore and 2-5SD for LGEgray compared to the normal area).

ROI: Region of interest

LGE: late gadolinium enhancement

Figure 3. Histopathological Image of the Fibrosis

LV myocardial specimens were stained with Elastica-Masson stain. The relative volume of myocardial muscle and fibrous tissue (arrow) was determined at a magnification of 100×. The fibrosis index was defined as the ratio of fibrosis tissue to the total myocardial field.

Figure 4. GLS and LGE before AVR

GLS was significantly correlated with LGEcore ($r=0.38$, $p<0.05$), LGEgray ($r=0.57$, $p<0.01$) and LGEcore+gray ($r=0.60$, $p<0.01$).

Figure 5. LGE and the Fibrosis Index before AVR

LGEcore ($r=0.62$, $p<0.05$) and LGEcore+gray ($r=0.61$, $p<0.05$), but not LGEgray, was significantly correlated with the fibrosis index.

Figure 6. GLS and the Fibrosis Index before AVR

GLS was significantly correlated with the fibrosis index ($r=0.68$, $p<0.05$).

Figure 7. Receiver-Operating Characteristics (ROC) Curve Analysis for Prediction of GLS Improvement after AVR

A) In the ROC analysis, the area under the curve was 0.81 for predicting postoperative GLS improvement (≥-19.9%) by LGEcore, with a cut-off value of 2.86g (sensitivity, 78.6%; specificity, 83.3%).

B) Patients with low LGEcore (<2.86 g) showed improvement in GLS after AVR compared to those with high LGEcore (≥2.86g).

Black circle: LGEcore <2.86g, white circle: LGEcore ≥2.86 g.

Table 1 Patient baseline characteristics (n=29)

Age, yrs	73 (66-78)
Men, n (%)	15 (52)
Height, cm	155.4 (148.2-161.7)
Body weight, kg	55.2 (51.8-60.5)
Body surface area, m^2	1.50 (1.41-1.60)
Body mass index, kg/m^2	22.8 (19.8-25.0)
NYHA functional class, n (%)	
I	20 (69)
II	8 (28)
III	1 (3)
IV	0
Symptoms, n (%)	
Dyspnea	9 (31)
Chest pain	4 (14)
Syncope	3 (10)
Risk factors, n (%)	
Hypertension	19 (66)
Diabetes mellitus	4 (14)
Hyperlipidemia	16 (55)
Current smoker	5 (17)
History/comorbidity, n (%)	
Chronic kidney disease	7 (24)
Cerebral vascular disease	3 (10)
Chronic obstructive pulmonary disease	3 (10)
Brain natriuretic peptide, pg/ml	85.0 (39.1-183.0)
eGFR, ml/min/1.73 m^2	68.0 (59.0-74.0)

Continuous variables are expressed as median (interquartile range).

NYHA: New York Heart Association, eGFR: estimated glomerular filtration rate.

Table 2 Preoperative echocardiographic and MRI parameters (n=29)

Echocardiography	
IVS, mm	13.1 (11.1-14.3)
PW, mm	12.9 (11.4-13.5)
LVDd, mm	41.7 (37.4-45.5)
LVDs, mm	25.4 (21.9-28.7)
LVEDV, ml	62.8 (54.1-77.1)
LVESV, ml	21.5 (17.2-28.7)
LV ejection fraction, %	65.7 (61.9-68.5)
LVMI, g/m^2	123.2 (113.0-148.6)
LAVI, ml/m^2	37.4 (25.7-48.8)
E/A	0.63 (0.51-0.82)
e', cm/sec	4.9 (4.4-6.2)
E/e'	12.4 (9.4-19.5)
Aortic valve	
Peak velocity, m/s	4.72 (4.30-5.25)
Mean PG, mmHg	51.0 (41.4-68.1)
Aortic valve area, cm^2	0.67 (0.57-0.79)
Zva, $mmHg/ml/m^2$	5.40 (4.53-6.50)
2D-GLS, %	-16.5 (-18.2- -14.2)
MRI	
LGEcore, g	3.0 (1.2- 6.7)
LGEgray, g	10.8 (7.3- 17.8)
LGEcore+gray, g	15.0 (9.5- 22.7)

Continuous variables are expressed as median (interquartile range).

IVS: interventricular septal thickness, PW: posterior wall thickness, LVDd: left ventricular end-diastolic diameter, LVDs: left ventricular end-systolic diameter, LVEDV: left ventricular end-diastolic volume, LVESV: left ventricular end-systolic volume, LVMI: left ventricular mass index, LAVI: left atrium volume index, PG: pressure gradient, GLS: global longitudinal strain, LGE: late gadolinium enhancement.

Table 3 Comparison of pre- and postoperative echocardiographic parameters (n=26).

	Pre-AVR	Post-AVR	P value
IVS, mm	13.1 (11.5-14.2)	10.8 (9.0-12.2)	<0.001
PW, mm	13.0 (11.6-13.4)	10.1 (9.0-11.6)	<0.001
LVDd, mm	41.5 (37.3-46.3)	43.0 (37.4-45.2)	0.76
LVDs, mm	25.6 (22.0-29.0)	25.7 (21.0-29.6)	0.80
LVEDV, ml	62.9 (54.4-78.7)	63.6 (56.3-79.7)	0.88
LVESV, ml	21.9 (17.3-31.2)	23.2 (19.5-30.2)	0.74
LV ejection fraction, %	65.6 (61.8-68.7)	65.6 (57.6-67.4)	0.34
LVMI, g/m^2	123.2 (113.1-142.3)	92.9 (81.1-110.0)	<0.001
LAVI, ml/m^2	35.5 (20.8-48.7)	30.6 (24.4-39.0)	0.28
E/A	0.62 (0.51-0.82)	0.91 (0.73-1.14)	0.014
e', cm/sec	5.2 (4.5-6.4)	7.5 (5.9-9.6)	0.001
E/e'	12.1 (8.8-14.5)	9.7 (8.1-14.2)	0.38
Peak velocity, m/s	4.73 (4.18-5.35)	2.55 (2.44-3.01)	<0.001
Mean PG, mmHg	50.5 (39.4-70.0)	14.1 (11.5-17.1)	<0.001
Aortic valve area, cm^2	0.65 (0.56-0.76)	1.47 (1.20-1.75)	<0.001
Zva, $mmHg/ml/m^2$	5.46 (4.98-6.51)	4.48 (3.37-5.04)	0.001
2D-GLS, %	-16.9 (-18.9- -14.2)	-19.9 (-22.1- -17.9)	0.004

Continuous variables are expressed as median (interquartile range).

AVR: aortic valve replacement, IVS: interventricular septal thickness, PW: posterior wall thickness, LVDd: left ventricular end-diastolic diameter, LVDs: left ventricular end-systolic diameter, LVEDV: left ventricular end-diastolic volume, LVESV: left ventricular end-systolic volume, LVMI: left ventricular mass index, LAVI: left atrium volume index, PG: pressure gradient, GLS: global longitudinal strain.

Table 4 Comparison of echocardiographic and MRI parameters between groups with or without GLS improvement

	Improvement group (n=14)	Non-improvement group (n=12)	P value
Age, yrs	73.0 (65.5-78.3)	72.5 (58.8-75.8)	0.71
Implanted valve size			0.26
19 mm, n	7	4	
21 mm, n	5	7	
23 mm, n	2	0	
27 mm, n	0	1	
Preoperative sBP, mmHg	117 (102-136)	121 (117-131)	0.71
Postoperative sBP, mmHg	126 (118-136)	131 (114-140)	0.56
Preoperative echocardiography			
IVS, mm	13.2 (12.1-14.7)	13.0 (10.5-14.0)	0.63
PW, mm	12.8 (11.6-13.6)	13.1 (11.5-13.5)	0.71
LVDd, mm	40.9 (37.5-42.2)	45.5 (37.0-50.3)	0.13
LVDs, mm	24.4 (19.5-27.7)	26.1 (22.8-32.0)	0.19
LVEDV, ml	60.8 (51.7-70.4)	69.5 (57.6-90.2)	0.11
LVESV, ml	19.2 (16.0-26.5)	25.3 (17.6-31.7)	0.25
LV ejection fraction, %	66.0 (60.5-70.1)	65.4 (62.4-67.2)	0.90
LVMI, g/m^2	118.9 (108.7-137.8)	127.7 (115.2-164.6)	0.37
LAVI, ml/m^2	37.4 (20.8-48.7)	33.5 (22.2-58.6)	0.98
E/A	0.62 (0.51-0.71)	0.68 (0.51-1.18)	0.35
e', cm/sec	5.3 (4.5-6.2)	5.2 (4.5-7.0)	0.94
E/e'	10.6 (8.4-14.5)	12.6 (10.1-18.2)	0.32

Peak velocity, m/s	4.73 (4.18-5.38)	4.75 (4.07-5.43)	0.98
Mean PG, mmHg	52.0 (40.8-76.8)	50.5 (38.1-68.6)	0.78
Aortic valve area, cm^2	0.64 (0.54-0.77)	0.66 (0.56-0.81)	0.67
SVi, ml/m^2	34.5 (25.6-35.6)	31.4 (24.6-36.0)	0.61
Zva, $mmHg/ml/m^2$	5.81 (4.10-7.07)	5.41 (4.99-6.27)	0.76
2D-GLS, %	-17.7 (-20.5- -14.9)	-15.2 (-18.1 - -12.7)	0.18
Postoperative echocardiography			
IVS, mm	9.7 (8.7-11.8) #	11.5 (9.9-13.4)	0.041
PW, mm	9.5 (8.6-10.6) #	11.1 (9.9-13.0)	0.036
LVDd, mm	43.0 (38.0-44.4)	41.8 (37.4-45.4)	0.86
LVDs, mm	24.9 (21.4-29.6)	25.7 (20.1-29.7)	0.82
LVEDV, ml	62.9 (55.1-79.7)	65.3 (55.9-81.9)	0.63
LVESV, ml	24.8 (17.6-30.6)	22.1 (20.4-29.2)	0.94
LV ejection fraction, %	65.2 (57.5-67.4)	65.5 (61.4-68.4)	0.82
LVMI, g/m^2	82.2 (74.5-101.2) #	102.7 (92.4-127.6) #	0.036
LAVI, ml/m^2	29.8 (22.9-34.1)	37.2 (24.1-52.2)	0.30
E/A	0.97 (0.79-1.25) #	0.9 (0.6-1.1)	0.32
e', cm/sec	8.5 (6.9-10.6) #	6.0 (5.1-8.0)	0.011
E/e'	9.2 (7.1-11.9)	11.6 (9.3-15.8)	0.044
Peak velocity, m/s	2.6 (2.5-3.1) #	2.5 (2.3-3.0) #	0.53
Mean PG, mmHg	15.7 (12.1-17.1) #	13.0 (11.2-17.7) #	0.49
Aortic valve area, cm^2	1.26 (1.12-1.61) #	1.60 (1.32-1.79) #	0.28
SVi, ml/m^2	35.1 (32.7-40.3) *	33.3 (24.7-40.1)	0.33
Zva, $mmHg/ml/m^2$	4.11 (3.39-4.78) #	4.42 (3.15-5.58)	0.33
2D-GLS, %	-22.1 (-22.4- -20.3) #	-17.6 (-18.7- -13.4)	<0.001
Preoperative MRI			

LGEcore, g	1.34 (0.81-2.98)	4.70 (2.99-9.00)	0.005
LGEgray, g	8.72 (4.40-13.48)	10.8 (10.1-18.8)	0.12
LGEcore+gray, g	9.62 (6.84-15.24)	18.8 (13.4-26.2)	0.013

sBP: systolic blood pressure, IVS: interventricular septal thickness, PW: posterior wall thickness, LVDd: left ventricular end-diastolic diameter, LVDs: left ventricular end-systolic diameter, LVEDV: left ventricular end-diastolic volume, LVESV: left ventricular end-systolic volume, LVMI: left ventricular mass index, LAVI: left atrium volume index, PG: pressure gradient, SVi: stroke volume index, GLS: global longitudinal strain, LGE: late gadolinium enhancement

*: $p<0.05$ vs. preoperative echocardiography

#: $p<0.01$ vs. preoperative echocardiography

Table 5 Multivariate analysis to predict postoperative improvement in GLS

	Univariate analysis		Multivariate analysis	
	β	P value	β	P value
Preoperative GLS	0.264	0.10		
LGEcore	0.446	0.011	0.446	0.022
LGEcore+gray	0.319	0.056		

GLS: global longitudinal strain, LGE: late gadolinium enhancement

Fig. 1

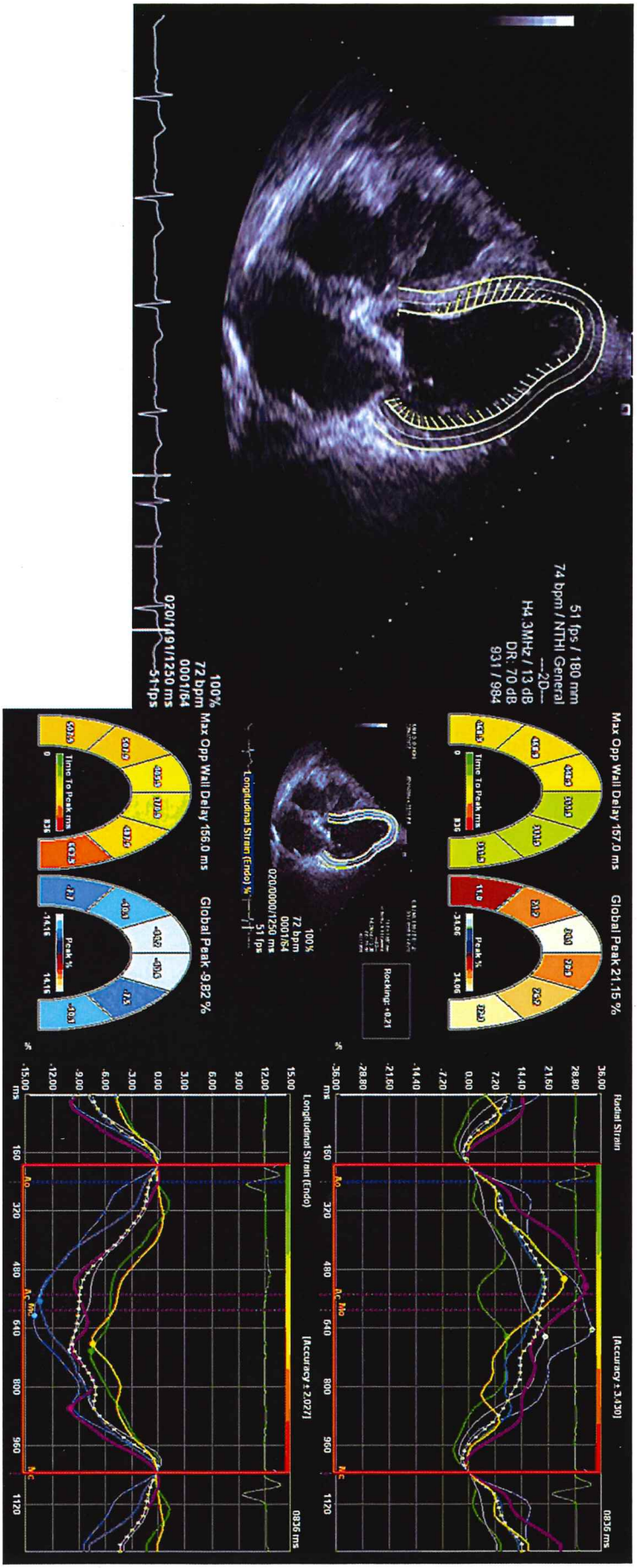
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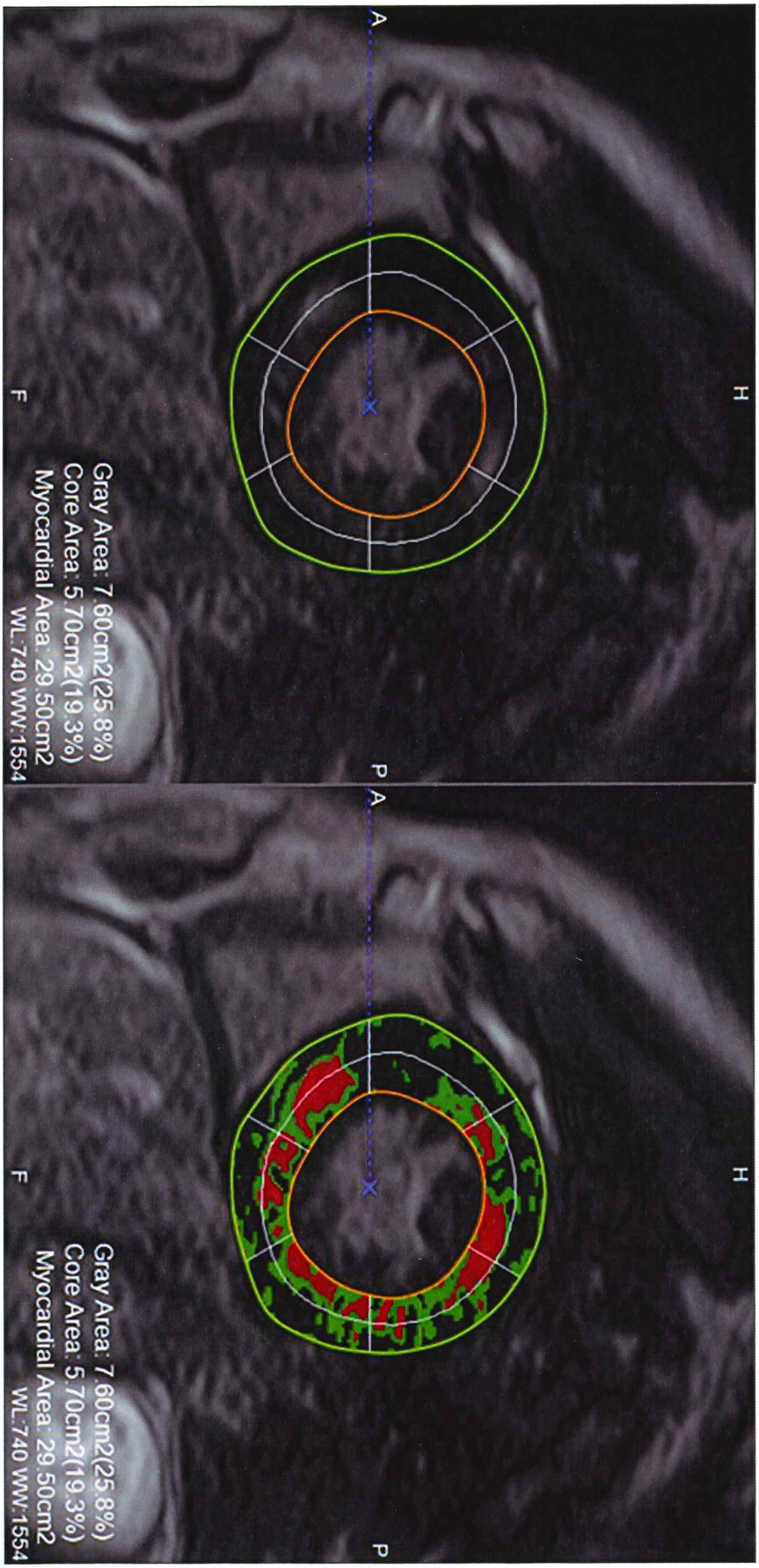
Fig. 2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Myocardial Area: 29.50cm2
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Fig. 3

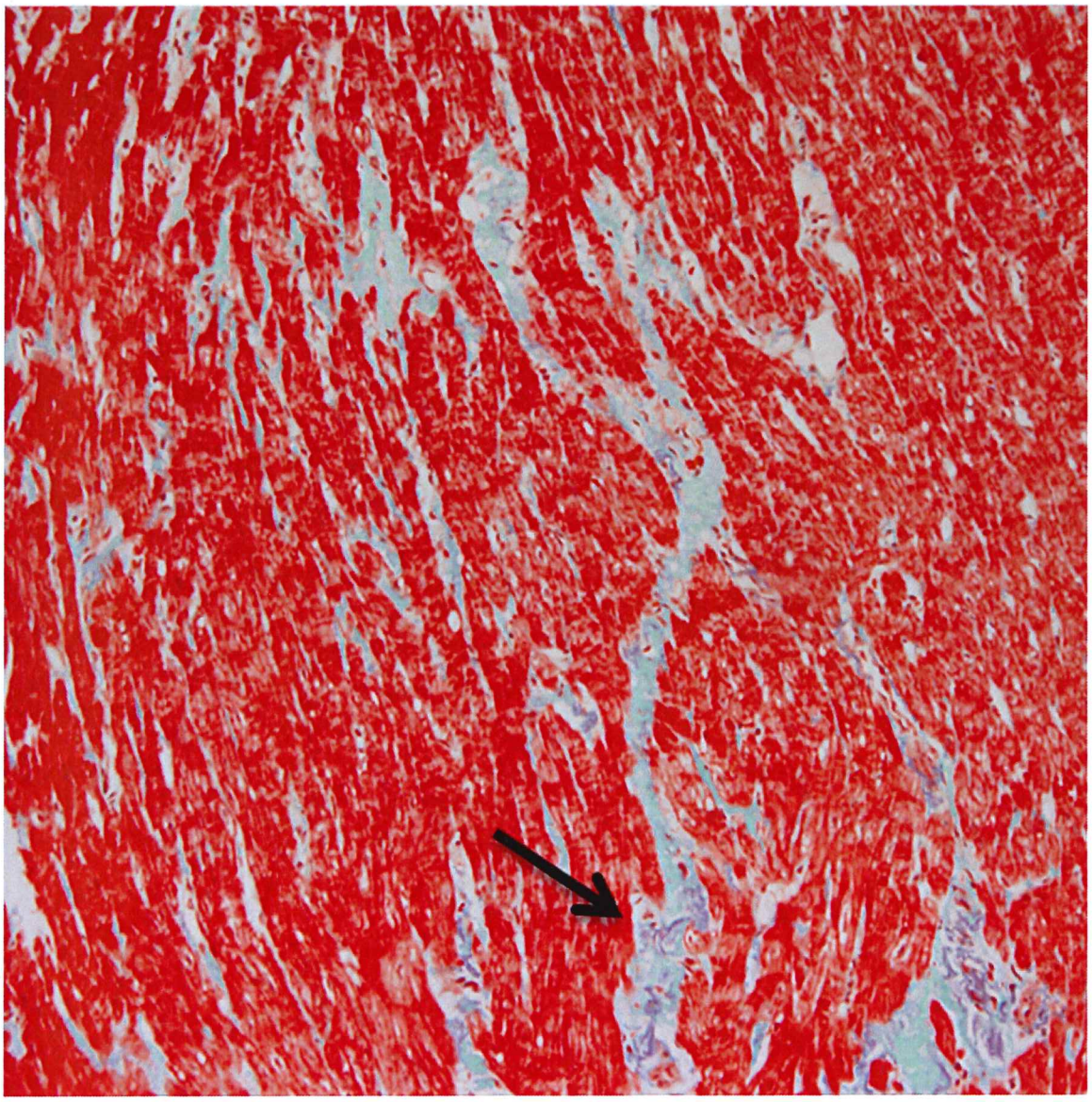


Fig. 4

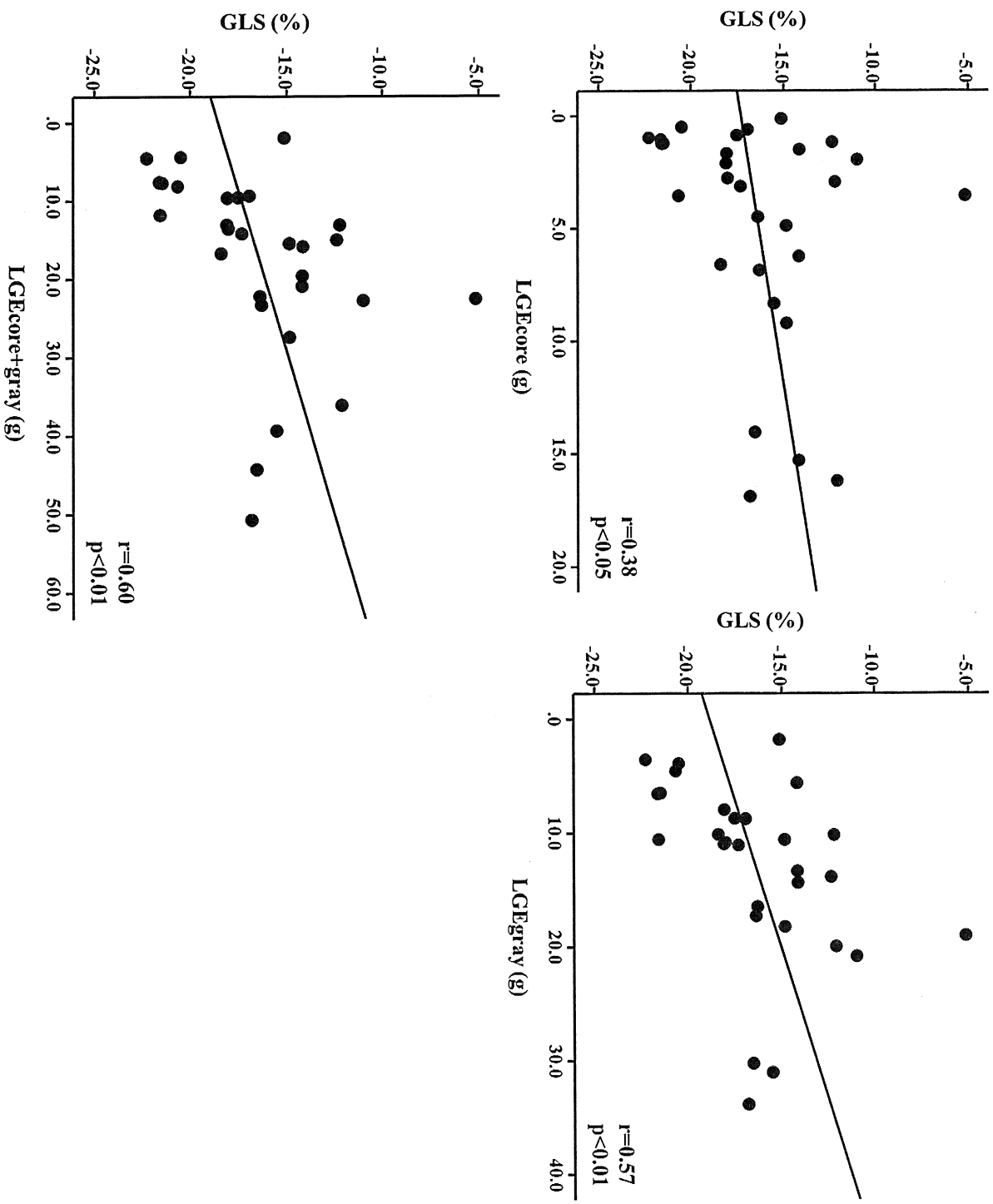

GLS (%)
-5.0
-10.0
-15.0
-20.0
-25.0
.0
5.0
10.0
15.0
20.0
LGEcore (g)
r=0.38
p<0.05
GLS (%)
-5.0
-10.0
-15.0
-20.0
-25.0
.0
10.0
20.0
30.0
40.0
LGEgray (g)
r=0.57
p<0.01
GLS (%)
-5.0
-10.0
-15.0
-20.0
-25.0
.0
10.0
20.0
30.0
40.0
50.0
60.0
LGEcore+gray (g)
r=0.60
p<0.01

Fig. 5

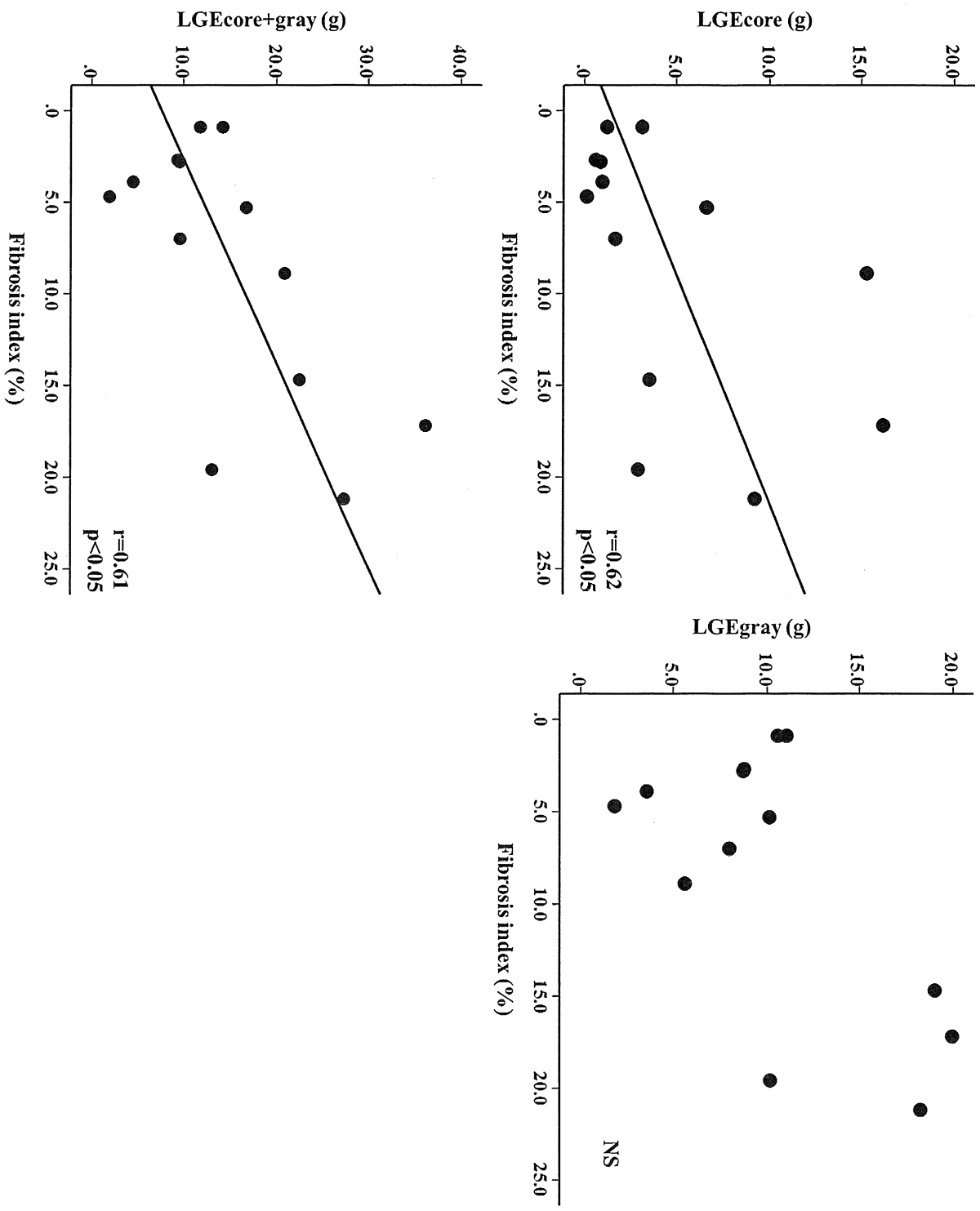

LGEcore+gray (g)
Fibrosis index (%)
r=0.61
p<0.05
LGEcore (g)
Fibrosis index (%)
r=0.62
p<0.05
LGEgray (g)
Fibrosis index (%)
NS

Fig. 6

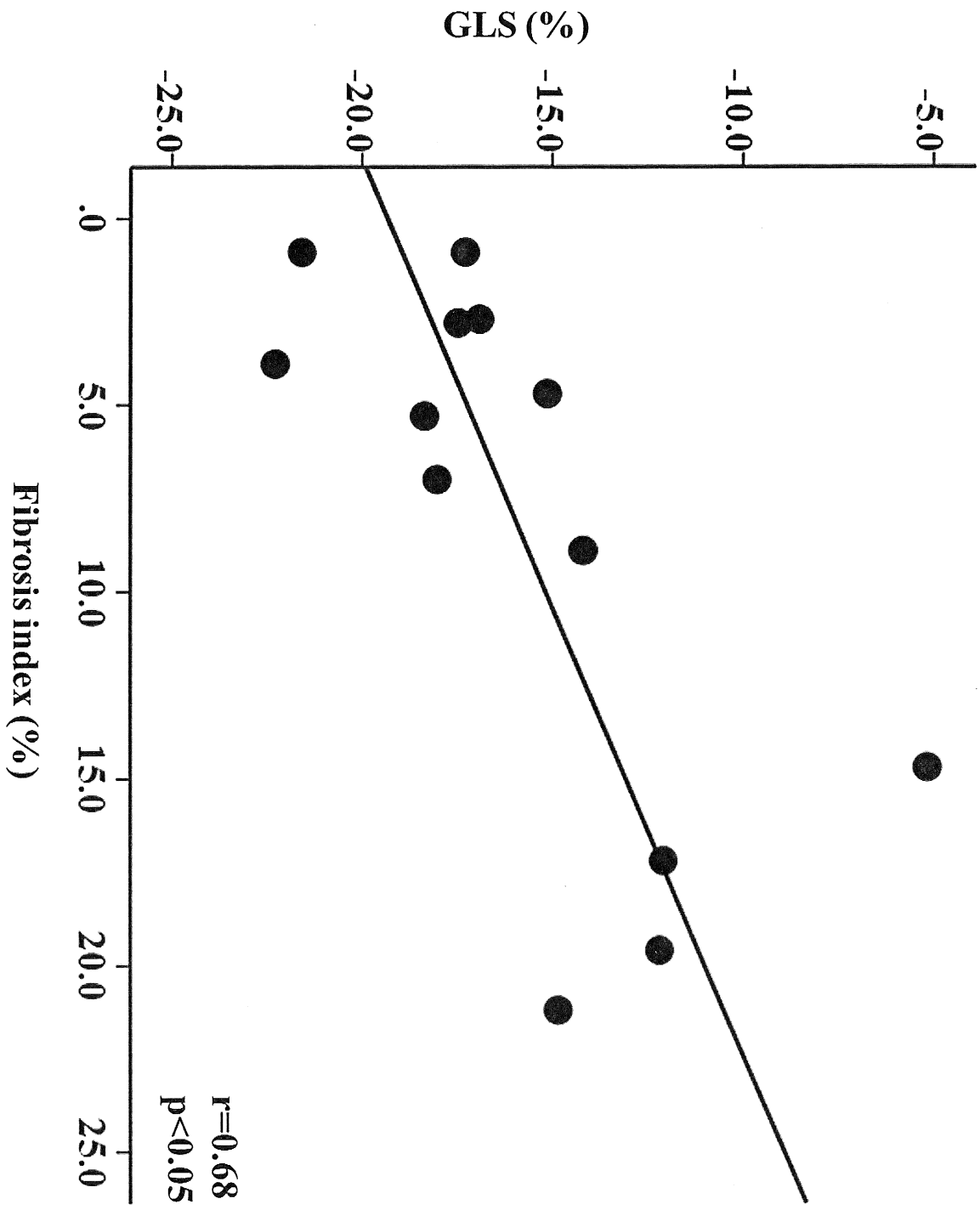
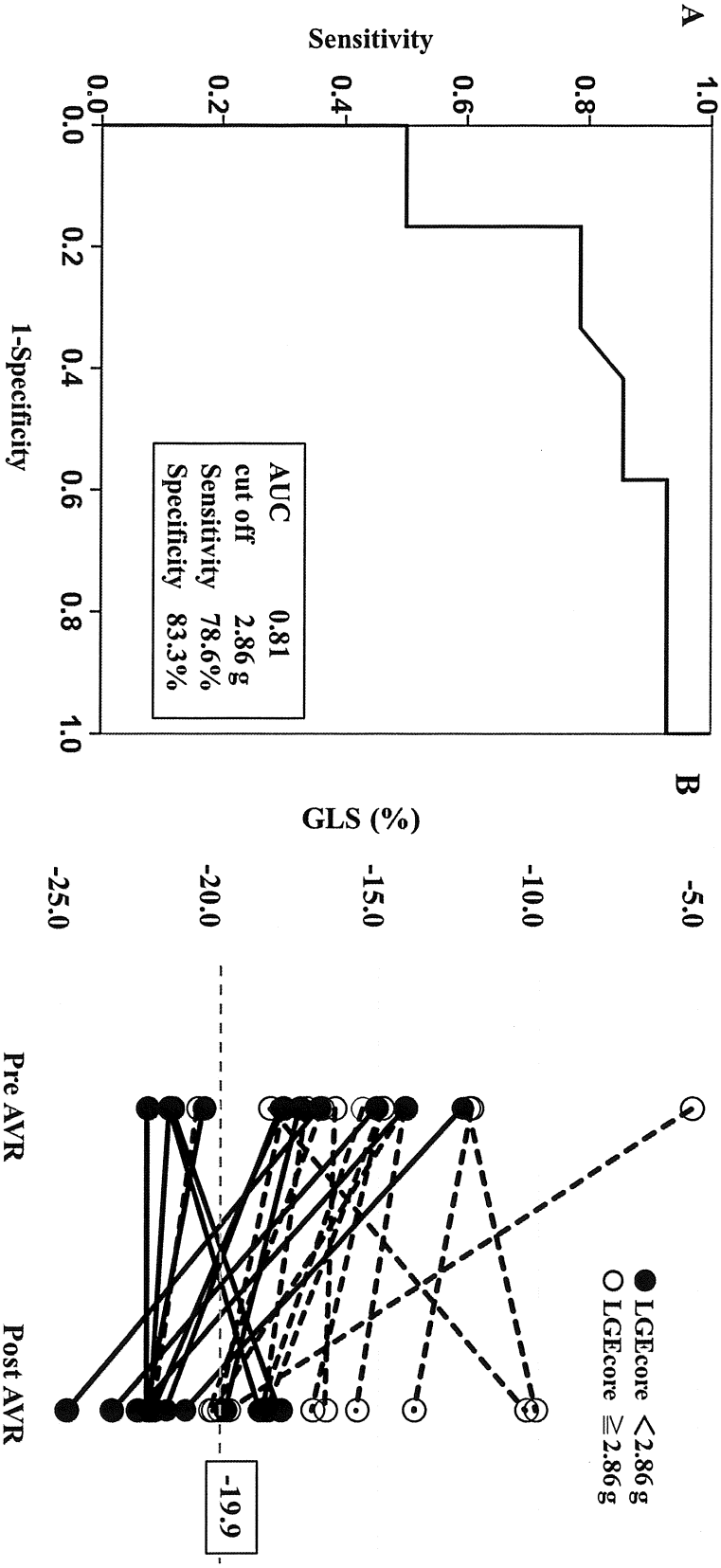

GLS (%)
-5.0
-10.0
-15.0
-20.0
-25.0
.0
5.0
10.0
15.0
20.0
25.0
Fibrosis index (%)
r=0.68
p<0.05

Fig. 7


A
Sensitivity
1.0
0.8
0.6
0.4
0.2
0.0
0.0
0.2
0.4
0.6
0.8
1.0
1-Specificity
AUC 0.81
cut off 2.86 g
Sensitivity 78.6%
Specificity 83.3%
B
GLS (%)
-5.0
-10.0
-15.0
-20.0
-25.0
Pre AVR
Post AVR
● LGEcore <2.86 g
○ LGEcore ≧2.86 g
-19.9