Evaluation of Left Ventricular Function in Patients with Mitral Annular Disjunction Using Speckle Tracking Echocardiography

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Abstract

Introduction: Mitral annular disjunction (MAD) is a structural abnormality characterized by the systolic detachment of the posterior mitral annulus and the ventricular myocardium. It is usually observed coexistent with mitral valve prolapse(MVP) and associated with a mechanical dysfunction despite preserved electrical isolation function of the mitral annulus. Diagnosis depends on the detection of disjunction by imaging modalities as transthoracic echocardiography or cardiac magnetic resonance imaging (CMRI). This study aimed to evaluate left ventricular (LV) function using speckle tracking echocardiography in MVP patients with MAD. Methods: This study was designed as a prospective, single-center study including 103 patients with MVP and 40 age- and sex-matched control subjects. Transthoracic echocardiography and cardiac magnetic resonance imaging were performed to assess LV function and MAD presence. Results: MAD (+) MVP (n=34), MAD (-) MVP (n=69), and control (n=40) groups were enrolled in the study. Among the MVP patients, 34 (33%) had MAD. T negativity in the inferior leads on electrocardiography was more frequent in the MAD (+) group than in the MAD (-) patients (4.3% vs 20.6%, p=0.014). Mitral regurgitation degree, Pickelhaube sign (17.6% vs. 1.4%, p=0.005), and late gadolinium enhancement frequency (35.3% vs. 10.6%, p=0.002) were significantly higher in MAD (+) patients. MAD (+) patients had significantly impaired global longitudinal strain (GLS) -23.1 \pm 2.1 vs. -23.5 \pm 2.3, P<0.001), basal longitudinal strain (BLS) (-19.6 \pm 1.5 vs -20.5 \pm 1.9, P < 0.001), and Mid-Ventricular Longitudinal Strain(MVLS) (-22.2±1.7 vs -23.2±2.2, P<0.001) when compared to MAD (-) MVP patients, despite similar LV ejection fraction. All these values of MVP patients were also significantly lower than the control group. The mean MAD distance was 7.8 ± 3.2 mm in MAD (+) patients. Patients with 2 or more symptoms were higher in the MAD (+) group than in the MAD (-) group (4.3% vs 44.1%, P<0.001). Conclusion: This study demonstrated a significant decrease in longitudinal strain in MVP patients with MAD, indicating myocardial dysfunction. These findings suggest that MAD may contribute to LV dysfunction and highlight the importance of early detection in younger patients. Further research is needed to explore the functional implications and long-term outcomes of MAD.

Introduction

Mitral annular disjunction (MAD) is a structural abnormality of the mitral valve apparatus that is characterized by a separation between the atrial wall of the mitral annulus and the ventricular myocardium (1). This relatively new entity has been increasingly recognized in cardiac imaging studies in recent years and it is shown to be associated with mitral valve prolapse, mitral regurgitation, arrhythmic events, and sudden cardiac death. Its prevalence is found to be over 8% in general population and this number reaches up to four fold in patients with mitral valve prolapse (2). Abnormal atrial attachment of the posterior leaflet and related systolic curling is observed in MAD which accompanies mechanical annular dysfunction (3). MAD may contribute to mitral valve dysfunction by altering the geometry of the mitral valve annulus or by disrupting the continuity of the subvalvular apparatus (4). Moreover, it has been suggested that MAD may be associated with myocardial dysfunction that can be detected by abnormal myocardial strain. Separation between the atrial wall of the mitral annulus and the ventricular myocardium may disrupt myocardial mechanics, leading to decreased strain (5). Additionally, there may be a direct effect of MAD on the mitral valve, leading to mitral regurgitation and increased afterload on the left ventricle, which may also contribute to myocardial dysfunction (2,5).

There are limited number of studies in the literature that examined the strain parameters in MAD and the information about this subject is not enough to define a particular pattern. In the present study, our aim was to investigate the impact of mitral valve prolapse (MVP) on myocardial strain parameters.

Material and Methods

Patient Population

Between September 2020 and October 2021, we conducted a prospective, single-center study including 103 patients with mitral valve prolapse (MVP) and 40 healthy age- and sex-matched control subjects. Age<18, history or symptoms of coronary artery disease, heart valve disease with a more-than-mild severity, reduced ejection fraction (EF[?]50), elevated systolic pulmonary arterial pressure (SPAP) at rest (>50 mm Hg), heart failure and/or atrial fibrillation were regarded as the exclusion criteria. The control group comprised age- and gender-matched healthy subjects. Medical history was obtained for all participants, and each subject underwent physical examination including body surface area (BSA). The local ethics research committee approved the protocol, and each subject signed an informed consent form. The study complies with the Declaration of Helsinki.

Transthoracic Echocardiography

Transthoracic echocardiography (TTE) examination was performed using the "Philips Epiq 7 echocardiography device X5-1 transthoracic probe" (Philips Epiq7; Philips Healthcare, Inc., Andover, MA, USA). The standard evaluation included M-mode, 2-dimensional, and Doppler studies according to the recommendations of the American Society of Echocardiography. The anatomy of mitral valve apparatus was systematically evaluated to identify prolapsing scallops and/or presence of a flail leaflet; trans esophageal echocardiography was performed when appropriate. Systolic movement of one or both leaflets [?] 2mm above the mitral annular plane was accepted as MVP. Although the patients were not divided according to the aetiology of MVP, most patients were having myxomatous MVP rather than fibroelastic deficiency (6). The location of the mitral annulus is identified in the long axis view by zooming on the mitral value at the maximum achievable frame rate. Subsequently, the images were scrutinized on a frame-by-frame basis to accurately view the mitral annulus and to quantify the width of the MAD trench in addition to the extent of the prolapsus depth. Along with these aspects, upper and lower limits of MAD were defined according the expert consensus statement on arrhythmic MVP and MAD (1). The LV end-diastolic and end-systolic diameters and volumes were measured and indexed to BSA, and EF was calculated using biplane Simpson's method. To assess LV geometry, end-diastolic relative wall thickness, LV mass/BSA (g/m^2) , and sphericity index were obtained. Indexed LA area and biplane volumes also were calculated. Myocardial function was assessed with two dimensional speckle tracking echocardiography with layer specific myocardial deformation quantitative analysis function. End diastole was defined with R wave peak in ECG and end systole was defined as aortic valve closing time. Endocardial borders were observed from end systolic 2-dimensional images. Wide myocardial width was calibrated and epicardial borders were evaluated. Mid zone speckles between epicardial and endocardial borders, mid myocardial border were defined automatically. Manual adjustments were carried out in order to obtain correct tracking and 2D speckle tracking width to cover all LV wall thickness if required. Peak systolic strain measurements were performed automatically in each segment via software analysis program (QLAB-CMQ software program of Philips Epiq 7C). Non-traceable segments were excluded after manual adjustment by the operator.

Cardiac magnetic resonance imaging (CMRI)

MAD diagnosis was confirmed with CMR analysis. Systolic displacement of mitral leaflet(s) at least 2 mm away from the annulus was determined as the lowest limit for diagnosis, as defined earlier (1). MAD length is measured in the sagittal views as the distance between the leaflet insertion on the detached annulus and the left ventricle border. All CMR examinations were performed on a 1.5T scanner (Aera Siemens Medical system, Erlangen,Germany) using a phased-array body coil. All patients were monitored during the procedure. The sequences were acquired using prospective cardiac gating. All acquisitions used balanced steady-state free precession cine sequence with the following typical parameters: TR/TE 3.8/1-3ms, slice thicknes 8mm with 2mm interclice gap, voxel size 1.8mmx1.8mmx6mm and acquired temporal resolution 40ms.

Statistical Analyses

All statistical tests were conducted using the Statistical Package for the Social Sciences 25.0 for Windows (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was used to analyze normality of the data. Continuous data are expressed as mean \pm SD, and categorical data are expressed as percentages. Student's t-test or Mann Whitney U test was used to compare unpaired samples as needed. Chi-square test was used to assess differences in categorical variables between groups. The relationships among parameters were assessed using Pearson's or Spearman's correlation analysis according to normality of the data. Primary analysis used ANOVA to compare all reported data for parametric variables, whereas Kruskall–Wallis test was used for comparison among non-parametric variables between the MAD subjects, MVP subjects and controls. Significance was assumed at a 2-sided p<0.05.

Results

The study included 103 patients with MVP and a control group of 40 people and 34 of these MVP patients (33%) had MAD. Patients were divided into groups as MAD (+) (n=34), MAD (-) (n=69) and control (n=40). The clinical and demographic characteristics of the study groups are shown in Table-1. There was no statistically significant difference between the groups in terms of gender, age, BMI, beta-blocker use and smoking habits. When symptom types such as palpitation, dyspnea, fatigue, chest pain and syncope were compared, no significant difference was found between MAD (+) and MAD (-) groups. However, number of symptoms on admission was not similar. Number of patients with 2 or more symptoms was higher in the MAD (+) group than in the MAD (-) group (4.3% vs 44.1%, p<0.001). T negativity in the inferior leads on electrocardiography was more frequent in the MAD (+) group than in the MAD (-) patients (4.3% vs 20.6%, p=0.014).

When the groups were compared in terms of echocardiographic and MRI findings (table 2), left ventricular ejection fraction (LVEF), posterior wall thickness (PW), interventricular septum to posterior wall ratio (IVS/PW), left ventricular end-diastolic diameter (LVEDD) and end-systolic diameter (LVESD), apical longitudinal strain (ALS) levels were similar. Mitral regurgitation degree (p=0.001), frequency of Pickelhaube sign (17.6% vs. 1.4%, p=0.005) and LGE (35.3% vs. 10.6%, p=0.002) were higher in MAD (+) patients compared to MAD (-) patients. When the left atrial volume index, TDI lateral Sa, global longitudinal strain (GLS), basal longitudinal strain (BLS), mid-ventricular longitudinal strain(MVLS) levels were compared, the difference between the 3 groups was statistically significant. GLS of the MAD (+) group was -23.1±2.1 and this was -23.5±2.3 for the MAD (-), -24.5±2.2 for the control group (p<0.001). BLS of the MAD (+), MAD (-) and control groups, these values were -22.2±1.7, -23.2±2.2 and -24.5±1.8; (p<0.001) and for MVLS, -22.2±1.7, -23.2±2.2 and -24.5±1.8 (P<0.001), respectively. The mean MAD distance was 7.8±3.2 mm in MAD (+) patients.

The relationship between GLS level and MAD distance in MAD (+) patients was evaluated by pearson correlation analysis (figure 1). It was observed that as the GLS level decreased, the MAD distance increased statistically significantly (r:0.694, p<0.001). Then, the relationship between BLS level and MAD distance in MAD (+) patients was evaluated by pearson correlation analysis (figure 2). It was observed that as the BLS level decreased, the MAD distance increased statistically significantly (r:0.715, p<0.001).

Discussion

The main finding of our study is the numeric decrease in longitudinal strain in MVP patients with MAD when compared to both MAD (-) MVP and control groups. This difference was detected for both global and segmental longitudinal strain. We interpreted this result as a reflection of partial loss of basal support during systole for the ventricular myocardium in significant MAD. The normal mitral annulus has roots located within the ventricular myocardium and these roots provide tight anchoring of the annulus to the ventricular myocardium (7). MAD occurs when these roots of the mitral annulus separate from the ventricular myocardium or fail to adhere sufficiently. However, the data about the functional implications of MAD and related ventricular dysfunction in the literature is scarce. First study in Medline about this subject was reported by Lee et al which investigated the 3D structure of MAD and its functional importance. In their study 42% of the 101 MVP patients were having MAD and mean dislodgement distance was 8.9 cm. Both results were compatible with ours. However, they found that although MVP had a reductive effect on left ventricular global longitudinal strain (LV-GLS) when compared to the control group with normal mitral valve, MAD positivity didn't have any additional effect on LV-GLS. This result was opposing our main finding. One of the main differences between our and their study population was age. Mean age of our and their MAD+ MVP groups were 35.7 ± 14.2 and 56 ± 13 respectively. A systematic review defining the features of MAD has revealed that average age of these patients was 62 years in the literature. Therefore, our study population is younger, mostly composed of Barlow's disease, suggesting that functional effects of MAD may show different characteristics according to the age period in which it is detected, and this may be due to etiological differences (8).

A case-control study by Wang et al examined the strain parameters of 21 MAD+ and 21MAD- MVP patients. MAD was causing a significant decrease in basal longitudinal strain by TTE, basal inferolateral (BIL), basal circumferential and basal radial strain by cardiac magnetic resonance imaging (CMR). Moreover, they concluded that global circumferential strain by CMR was independently associated with the diagnosis of MAD. They claimed the difference between TTE and CMR as the TTE strain analysis couldn't catch the significant difference in strain parameters of MAD+ and MAD- MVP patients however CMR could. These results may be attributable to some confounding factors as the relatively small sample size and study design. In our study, all the strain differences were found by TTE evaluation (5). More recently, Sanoglioni et al analyzed 93 MVP patients, 34.4% of which were MAD+ and showed significantly impaired LV-GLS (-17.2 \pm 1.4 vs -19.4 \pm 3.0%, p < 0.001) and LV-GCS (-16.3 \pm 4.1 vs -20.4 \pm 4.9, p < 0.001) in MAD+ MVP patients compared to MAD- MVP cases, despite similar LV ejection fraction (9).

In our study 103 MVP patients and 40 control subjects were included and MAD was detected in 34(33%) of the MVP patients, compatible with most other studies in the literature. MAD is detected in 20 to 58 percent of the patients diagnosed with MVP and the prevalence is even higher in myxomatous MVP (1). Nonetheless, 21% of MAD patients don't have MVP (4). In our study, all MAD patients were having MVP.

Our results provided that longitudinal strain is significantly affected in MAD+ patients when compared to MAD- MVP patients. Longitudinal strain and especially the GLS provides information about the functioning of longitudinal fibres and LV remodelling. It is known to be a predictor of cardiovascular outcome (10). Therefore our results are important in terms of detecting early myocardial dysfunction related to MAD especially in the younger patients. Moreover, in our study MVP patients with MAD had more severe mitral insufficiency when compared to the MAD-group. This result may be explained by the changes observed in annulus dynamics in patients with MAD. The mitral annulus enlarge more at the end of the systole (paradoxical systolic dilatation) and flattening of the annulus rather than physiologic saddling (paradoxical annular unsaddling) is a feature of MAD. It has been shown that MAD is associated with deformity of mitral leaflets and chordae tendienae. Furthermore, extend of disjunction and degree of mitral regurgitation are shown to be correlated (8). Likewise, Dumont et al have proved that annular dilatation due to MAD+ Barlow's mitral valve disease causes more severe mitral regurgitation (11).

All the above mentioned features of MAD positivity in patients with MAD also may explain the increased number of symptoms in this group, another finding of our study, when compared to MAD- group, owing to more severe functional deformation.

Malignant MVP is characterized with increased sudden cardiac death risk, bileaflet prolapse, ECG repolarization abnormalities, papillary muscle and inferobasal wall fibrosis and its main echo finding is MAD. This entity also includes another term arrhythmic MVP (AMVP) which usually presents with frequent premature ventricular contractions and T-wave inversion in the inferolateral leads (12). Although we didn't define a subgroup as malignant MVP of AMVP, our results were compatible with the literature such that T wave inversion in the inferolateral leads was detected in 20.6% of MAD+ group which was significantly more common than the MAD (-) group (4.3%) (P=0.014). LV fibrosis especially at the papillary muscles and inferobasal wall of the left ventricle can be detected as late gadolinium enhancement(LGE) in patients with MAD and previous reports showed that LGE can be seen as high as 40-47% of these patients (5,13). Likewise, in our study 35.3% of MAD+ MVP patients had LGE in CMR whereas this percentage was only 10% for MAD- MVP patients. Actually these areas of LGE in MAD+ MVP patients were found to be related with unipolar low voltage areas which are accepted as a potential substrate for ventricular arrhythmias(VA) and sudden cardiac death(SCD) (14). This relationship between LGE and VA and SCD in patients with MVP was also supported by other studies (3,15).

Another important finding of our study was the higher frequency of Pickelhaube sign in MAD+ MVP patients. This sign is a high velocity mid-systolic spike gathered from the lateral mitral annulus by tissue Doppler imaging, due to the stretching effect of prolapsing leaflet on posteromedial papillary muscle. As LGE, this sign was found to be a noninvasive imaging marker associated with SCD in MVP in previous studies (16).

We detected this sign in 17.6% of MAD+ MVP patients whereas only %1.4 of the MAD- MVP group had this sign on TTE.

In our study, mean disjunction distance was 7.8 ± 3.2 mm There is no limit to define the movement of annulus as disjunction. In fact, detachment of the mitral annulus from myocardium may range between a few millimeters to more than 1 centimeter in the literature (17). Increased distance also increases the risk of SCD and it is reported that disjunction > 8.5 mm was predictive of VA (18).

Study limitations

Relatively small sample size, observational cross-sectional design additional to the lack of blinding and long term follow-up of the clinical outcomes are the main limitations of our study. The subjects were recruited from a single center, which may be associated with a selection bias. Although performed by experienced professionals, the echocardiography and cardiac magnetic resonance imaging (CMRI) techniques used to assess myocardial function and measure mitral annular disjunction (MAD) have inherent limitations and potential variability in measurements. More comprehensive strain analysis may provide a more precise assessment of left ventricular function. Limited information on MAD aetiology is another limitation since different aetiologies or underlying mechanisms of MAD could influence the study outcomes and interpretation of the results.

Conclusion

MAD is a structural abnormality of the mitral annulus which is usually accompanying mitral valve prolapse. Our study suggests that MAD may impair both regional and global LV functions that can be detected with strain analysis. We conclude that longitudinal strain parameters are affected and T wave inversion in ECG, increased dislodgement distance and LGE are important parameters that can inform about more severe MVP cases with MAD. MAD is a relatively new entity and further studies are necessary to determine the optimal management strategy for patients with MAD.

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Declaration of Conflict of Interest: All the authors declare no conflict of interest.

Data Availability Statement : Data supporting the findings of this study are available from the corresponding author on request.

Ethics Approval Statement: The local ethics research committee approved the protocol.

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Paremeters	$\begin{array}{l} \text{Control} \\ \text{group (n} \\ = 40) \end{array}$	$\begin{array}{l} \text{Control} \\ \text{group (n} \\ = 40) \end{array}$	${f MAD}\ (-)\ (n=69)$	MAD (-) (n = 69)	${f MAD}\ (+)\ (n{=}34)$	${f MAD}\ (+)\ (n{=}34)$	${f MAD}\ (+)\ (n{=}34)$	P (between groups)	P (between groups)
Age, years	Age, years	35.7±13.7	35.7±13.7	35.7 ± 14.2	35.7 ± 14.2	$36{\pm}12.7$			0.993
$\begin{array}{l}\text{Male,}\\ n(\%)\end{array}$	$\begin{array}{l}\text{Male,}\\ n(\%)\end{array}$	10(25)	10(25)	25(36.2)	25(36.2)	17(50)			0.084
$\overline{BMI},$ (kg/m^2)	$\overline{BMI},$ (kg/m^2)	$\begin{array}{c} 24.6\ \pm\\ 4\end{array}$	$\begin{array}{c} 24.6 \ \pm \\ 4 \end{array}$	23.3±3.6	23.3±3.6	23.5 ± 3.8			0.258
Smoker, $n(\%)$	Smoker, $n(\%)$	14(35)	14(35)	19(27.5)	19(27.5)	9(26.5)			0.650
Beta Blocker, n(%)	Beta Blocker, n(%)	-	-	13(18.8)	13(18.8)	7(20.6)			0.833

Tablo-1. The demographic and clinical data of the study population

Paremeters	$\begin{array}{l} \text{Control} \\ \text{group (n} \\ = 40) \end{array}$	$\begin{array}{l} \text{Control} \\ \text{group (n} \\ = 40) \end{array}$	${f MAD}\ (-)\ (n=69)$	MAD (-) $(n = 69)$	${f MAD}\ (+)\ (n{=}34)$	${f MAD}\ (+)\ ({ m n=}{ m 34})$	${f MAD}\ (+)\ ({ m n=}{ m 34})$	P (between groups)	P (between groups)
Symptoms	Symptoms								
and	and								
Signs	Signs								
Palpitation n(%)	, Palpitation, n(%)	-	-	41(59.4)	41(59.4)	20(58.8)			0.954
Fatique,	Fatique,	-	-	11(15.9)	11(15.9)	4(11.8)			0.572
n(%)	n(%)								
Chest	Chest	-	-	22(31.9)	22(31.9)	9(26.5)			0.573
Pain,	Pain,								
n(%)	n(%)								
Dyspnea,	Dyspnea,	-	-	16(23.2)	16(23.2)	9(26.5)			0.715
n(%)	n(%)								
Syncope	Syncope	-	-	1(1.4)	1(1.4)	3(8.8)			0.104
, n(%)	, n(%)								
2+	2+	-	-	3(4.3)	3(4.3)	15(44.1)			$<\!0.001$
symp-	symp-								
tom,	tom,								
n(%)	n(%)								
Inferior	Inferior	-	-	3(4.3)	3(4.3)	7(20.6)			0.014
lead T	lead T								
nega-	nega-								
tivity,	tivity,								
n(%)	n(%)								

Abbreviations: MAD, Mitral Annular Disjunction; BMI, body mass index;

Tablo 2: Echocardiography and MRI findings of the study population

	Control group $(n =$			
Paremeters	40)	$MAD \ (\text{-}) \ (n = 69)$	$MAD \ (+) \ (n = 34)$	$P(between \ groups)$
Ejection fraction,	64.7 ± 8.5	$62.6 {\pm} 8.9$	$62.5 {\pm} 6.6$	0.371
(%)				
IVS/PW	$0.95{\pm}0.16$	$0.99{\pm}0.16$	1.0 ± 0.19	0.311
PW, (mm)	$0.95{\pm}0.16$	$0.99{\pm}0.16$	$0.98{\pm}0.17$	0.021
LVEDD, (mm)	48.7 ± 7.5	45.5 ± 8.0	47.9 ± 8.2	0.091
LVESD, (mm)	32.3 ± 5.9	30.1 ± 7.5	$30.7 {\pm} 4.7$	0.231
MR Degree	-	0 (0-1)	1(1-2.2)	0.001
(25-75 p)				
LAVI (ml/mm^2)	$37.1 \pm 11.1^{* a}$	$49.2 \pm 18.1^{* e}$	$60.8 \pm 23^{a\ e}$	$<\!0.001$
TDI Lateral Sa	$10.7 {\pm} 1.6^{* a}$	$12.3 \pm 2.7^{* e}$	$14.5 \pm 3.1^{a e}$	$<\!0.001$
$(\mathrm{cm/s})$				
GLS, (%)	$-24.5\pm2.2^{* a}$	$-23.5\pm2.3^{*}$ e	$-23.1\pm2.1^{a\ e}$	$<\!0.001$
BLS, (%)	$-23.3 \pm 1.2^{* a}$	$-20.5 \pm 1.9^{* e}$	$-19.6 \pm 1.5^{a e}$	$<\!0.001$
MVLS, $(\%)$	$-24.5 \pm 1.8^{* a}$	$-23.2\pm2.2^{* e}$	-22.2±1.7 ^{a e}	$<\!0.001$
ALS, (%)	-26.9 ± 3.6	-27.9 ± 3.7	-27.5 ± 3.9	0.439
Pickelhaube sign,	-	1(1.4)	6(17.6)	0.005
n(%)				

	$Control\ group\ (n=$			
Paremeters	40)	$MAD \; (-) \; (n = 69)$	$MAD \ (+) \ (n = 34)$	$P(between \ groups)$
LGE, $n(\%)$	-	7(10.1)	12(35.3)	0.002
MAD distance	-		7.8 ± 3.2	
(mm)				

*P <0.05 Between control and MAD (-) groups, aP <0.05 between control and MAD (+) groups, eP <0.05 between MAD (-) and MAD (+) groups.

Abbreviations: MRI, Magnetic Resonance Imaging; MAD, Mitral Annular Disjunction; IVS, interventricular septum; PW, posterior wall; LVEDD, left ventricle end diastolic diameter; LVESD, left ventricle end systolic diameter; LAVI, Left Atrial Volume Index; TDI, Tissue Doppler Imaging; Sa, Systolic Annular; GLS, Global Longitudinal Strain; BLS, Basal Longitudinal Strain; MVLS, Mid-Ventricular Longitudinal Strain; ALS, Apical Longitudinal Strain; ; LGE, Late Gadolinium Enhancement.



Figure 1. The relationship between GLS level and MAD distance.



Figure 2. The relationship between BLS level and MAD distance.