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Usefulness of three-dimensional spherical index to assess different types of left ventricular remodeling

A meta-analysis

Decai Zeng, MD, Hui Chen, MD, Chun Lan Jiang, MD, Ji Wu, MD, PhD*

Abstract

Background: Left ventricular (LV) remodeling after myocardial injury, volume or pressure overload is characterized by a change in LV shape from an ellipse to more of a sphere. The usefulness of 3-dimensional (3D) sphericity index (SpI) for accurate evaluation of LV remodeling remains uncertain despite extensive research.

Methods: We searched Pubmed, Embase, Web of Science, and Cochrane databases to identify relevant studies from January 1, 1990 to August 1, 2016. The quality of each study was evaluated using the Newcastle-Ottawa Scale. Meta regression and sensitivity and subgroup analyses based on patterns of LV remodeling were performed.

Results: Thirteen studies with a total of 1064 patients were included in this meta-analysis. There was evidence of obvious heterogeneity ($I^2 = 82.4\%$; $P < .001$), which was mainly accounted for by the pattern of remodeling according to meta-regression. The result of subgroup meta-analyses suggested that SpI in patients with eccentric remodeling was significantly higher compared with control group (95% confidence interval [CI], 0.78–1.10). No statistic difference was found in LV SpI between healthy controls and patients with concentric hypertrophy (95% CI, −0.89 to 0.16) or myocardial injury (95% CI, −0.13 to 0.41).

Conclusion: 3D SpI can be widely used to assess LV remodeling in patients with eccentric remodeling, but has limitations in predicting concentric hypertrophy and regional or chronic myocardial injury.

Abbreviations: 2D = two-dimensional, 3D = three dimensional, AMI = acute myocardial infarction, AR = aortic regurgitation, AS = aortic stenosis, CI = confidence interval, DM = diabetes mellitus, HBP = high blood pressure, LV = left ventricular, LVEDV = left ventricular end-diastolic volume, MD = myotonic dystrophy, MR = mitral regurgitation, MRI = magnetic resonance imaging, NAMI = non-acute myocardial infarction, NOS = Newcastle-Ottawa-scale, OB = obesity, RF = renal failure, SMD = Standard mean difference, SpI = sphericity index, SLE = systemic lupus erythematosus.

Keywords: left ventricular remodeling, sphericity index, three-dimensional echocardiography

1. Introduction

Left ventricular (LV) remodeling describes changes in molecular, cellular, and interstitial structure, which trigger shape and functional remodeling that usually evolve after various kinds of myocardial injury or overload.[1] There are 3 major patterns: concentric remodeling usually associated with pressure overload from hypertension, which leads to growth in cardiomyocyte thickness; eccentric hypertrophy usually associated with volume overload from valvular regurgitation, which produces myocyte lengthening; and various myocardial injuries.[2] The common features are increased cardiomyocyte mass, sarcomere rearrangement, extracellular matrix deposition, inflammatory signaling, and immune cell activation, which finally lead to heart failure and even death if not attenuated or reversed by intervention.[3,4] Therefore, a more precise and early detection of LV remodeling is crucial for the clinical evaluation, diagnosis, management, and prognosis.

Echocardiography is widely used for noninvasive analysis of LV structure and geometry in patients with heart disease, as it is an inexpensive, radiation-less, and convenient technique with real-time visuals compared with magnetic resonance imaging (MRI) and computed tomography.[5] However, it does not accurately reflect real LV that is distorted in shape by 2D echocardiography, as it is affected by foreshortening in image acquisition and geometrical assumption. Additionally, 2D echocardiography cannot provide adequate information about discrete changes in regional shape and global dilation. 3D echocardiography facilitates the analysis of the geometric modification of heart.[6] It can also effectively surmount these limitations with the use of full-volume technique, which will significantly improve the accuracy of measurement, and is close to the current criterion standard MRI.[7] Sphericity index (SpI) as a novel parameter for quantitative assessment of geometric modification of LV relates the ventricular volume to the hypothesis that LV volume develops from an ellipse to more of a sphere after remodeling. This concept was first proposed

* Correspondence: Ji Wu, The First Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi 530021, China (e-mail: gxnnwuji@126.com).

around 30 years ago by Tomlinson.[8] Mannaerts et al use 3D echocardiography to differentiate patients with and without subsequent development of LV remodeling after acute myocardial infarction (AMI) on the basis of the 3D SpI.[9] Since then, this parameter has been applied to various types of LV remodeling.[10–12] Presently, despite much published research on SpI, there is a controversy over the change of SpI in LV remodeling. The objective of this study was to conduct a meta-analysis to explore the differences in 3D SpI between healthy subjects and patients with LV remodeling and identify the reasons that may contribute to the differences in reported data.

2. Materials and methods

This study is a meta-analysis; all pooled analyses are based on data in the literatures, and thus no information consent and ethical approval are required.

2.1. Literature search

All eligible articles published before August 30, 2016 were searched in Pubmed, Embase, Cochrane databases, and Web of Science using the following medical subject headings: "ventricular remodeling", "hypertrophy, left ventricular", "myocardial remodeling", "myocardial deformation", "heart remodeling", "cardiac remodeling", "ventricular dilation", "ventricular hypertrophy", "ventricular enlargement", "left ventricular shape", "left ventricular geometry", "sphericity index", "spherical index" and "shape index". Reference lists used in the eligible articles were also manually searched for potential sources.

2.2. Inclusionand exclusion criteria

Studies were considered eligible if fulfilled all of the following criteria: case-control or cohort studies about SpI in assessing LV remodeling; all studies evaluated SpI in adults older than 18 years with a diagnosis of LV remodeling based on clinical information and imaging data; 3D echocardiography was performed and LV volume measured by 3D LV analysis software. Studies were excluded if they were: unrelated to assessment of LV remodeling;

insufficient data or duplicated publish; article types such as case report, reviews, meta-analysis, or letters; not human clinical studies.

2.3. Data extraction

Two authors independently extracted data from the eligible studies including the following information: the first author, publication year, country, etiology of LV remodeling, sample size, sex ratio, age, type of study design, 3D ultrasound system and 3D SpI (Table 1). Disagreements between 2 authors were resolved by discussion.

2.4. Quality assessment

The quality of the included studies was assessed by 2 authors independently based on the Newcastle-Ottawa-scale (NOS) in this meta-analysis.[26] NOS uses a star rating system to determine the quality of studies based on 2 categories which comprise selection of participants, comparability between groups, and assessment of exposure or outcome. NOS is widely used and recommended by the Cochrane collaboration to assess the quality of nonrandomized studies especially in cohort and case-control studies. Eight items relevant to the evaluation of quality were applied to this meta-analysis with star ratings from 0 to 9. The quality of included studies was divided into 3 classes: low (0–3 stars), medium (4–6 stars), and high (7–9 stars). Disagreements were resolved through discussion.

2.5. Statistical analysis

We performed this meta-analysis using Stata12.1 software (Stata Corp, College Station, TX) in a random-effect/fixed-effect model. Heterogeneity test would be conducted to explore heterogeneity among studies by using χ^2-based Q test and I^2 test. I^2 values range from 0% to 100% representing the proportion of variability among studies that can contribute to heterogeneity instead of sampling error.[27] The pooled standardized mean differences and 95% confidence interval (CI) were calculated by a fixed-effects model if no significant heterogeneity ($P > .1$ and $I^2 <$

Table 1

Baseline characteristics of included studies.

Reference	Year	Country	n		Male/female		Age, year		Etiology	3D system
			Case	Control	Case	Control	Case	Control		
Cong et al[13]	2015	China	68	40	0/68	0/30	29±4	30±5	Trimester 1; trimester 2; trimester 3	GE Vivid E9
Yang and Zeng[14]	2015	China	27	46	15/12	28/18	54±15	58±10	AR	GE Vivid E9
			20		15/5		54±18		AS	
			20		14/6		58±7		HBP	
			20		NR		NR		DM	
			20		14/6		58±11		AMI	
			20		14/6		62±8		NAMI	
Enache et al[15]	2015	Romania	60	55	50/10	41/14	46±16	43±15	AR	GE Vivid E9
Monte et al[16]	2014	Italy	30	30	14/16	17/13	35±11	37±12	OB	GE Vivid 9
Huang et al[17]	2014	china	34	34	4/30	5/29	31±8	34±10	SLE	GE Vivid E9
Kovacs et al[18]	2014	Hungary	44	46	24/20	22/24	48±13	48±12	RF	GE Vivid E9
De Stefano et al[19]	2013	Italy	21	21	NR	NR	34	34	MD	NR
Nakai et al[20]	2012	USA	79	20	63/16	11/9	64±15	58±13	MR	Philips IE33
Vieira et al[21]	2011	Brazil	23	20	17/6	NR	57±13	NR	MI	NR
Muraru et al[22]	2011	Italy	18	18	NR	NR	45±8	45±8	MI	GE Vivid E9
Li et al[23]	2008	China	62	30	44/18	20/10	59±13	55±18	AMI	Philips sonos 7500
Marisa et al[24]	2006	Italy	92	52	75/17	26/26	65±9	43±14	MI	GE Vivid 7
Wong et al[25]	2001	USA	79	8	NR	4/4	NR	39±17	MR1~2+; MR3~4+	HP 5500

Data are expressed as number of patients or mean±SD. AR=aortic regurgitation, AMI=acute myocardial infarction, AS=aortic stenosis, DM=diabetes mellitus, HBP=high blood pressure, MD=myotonic dystrophy, MR=mitral regurgitation, NAMI=non-acute myocardial infarction, NR=not reported, OB=obesity, RF=renal failure, SLE=systemic lupus erythematosus.
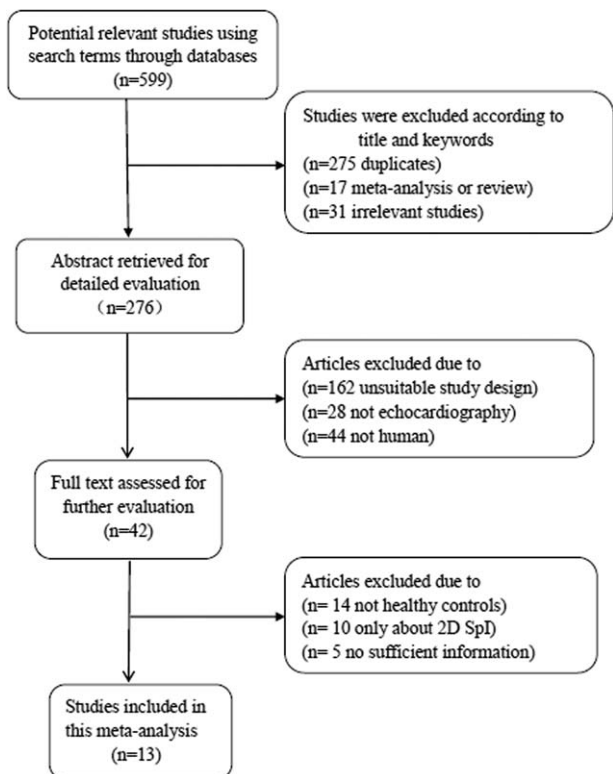
Figure 1. Flow chart of literature searched and process of study selection.

50%) was found. Otherwise, a random-effects model would be used. Sources of heterogeneity were studied by sensitivity analysis and meta-regression. A sensitivity analysis was performed by removing single study in turn to identify whether inclusion of studies had a significant impact on pooled values. Meta-regression was used to estimate ≥1 covariates with values defined for each study to explain heterogeneity. Publication bias was evaluated using funnel plots and Egger linear regression test. In funnel plots, each dot represents a study. All dots symmetric distribution on both sides of the line suggested there was no obvious publication bias. Otherwise, it was determined that publication bias existed.

3. Results

3.1. Characteristics of the included studies

The literature search identified 599 citations (Pubmed 179, Embase 285, Cochrane databases 28,Web of Science 107), of which 586 were excluded based on the aforementioned exclusion criteria after review of title, abstract, and full text. Thirteen studies with a total of 1094 patients fulfilled the inclusion criteria and were included in this meta-analysis. The detailed process was shown in a flow chart (Fig. 1). Baseline patient characteristics of studies included in the meta-analysis are shown in Table 1. The publication dates range from 2001 to 2015. Four studies were performed in the Asia, 6 in Europe, and 3 in the United States. The average age of patients ranged from 29 to 65 years. Of the 13 studies, 10 were case-control studies, and 3 were cohort studies. The patients in the studies selected for this meta-analysis were under different pathophysiologic conditions. In 5 articles, myocardial infarction (MI) was diagnosed that caused a series of complicated adverse effects, including regional expansion in infarctive zone, and late entire ventricular enlargement induced by volume and pressure overload. Patients in 4 studies suffered from valvular disease. One study focused on LV remodeling in patients with high blood pressure, diabetes mellitus, obesity, systemic lupus erythematosus, renal failure, and myotonic dystrophy. One study aimed to investigate LV performance during each pregnancy trimester. 3D SpI was measured in 7 studies using commercially available software equipped with auto 4D auto LV quantification technique. Measurements of LV volume in 1 study were performed using 3D LV analysis volume software (TomTec Imaging Systems, Unterschleisheim, Germany). Harmonic real-time transthoracic 3D imaging was performed in 1 study using a commercial ultrasound imaging system (iE33, Philips Medical Systems, Andover, MA). The remaining 4 studies did not report 3D LV analysis software. The results of quality assessment of included studies were shown in

Table 2

Quality assessment of the 13 studies were ultimately included in this meta-analysis based on the Newcastle-Ottawa Scale.

| | For case-control studies | | | | | | | | |
| | Selection | | | | Comparability | | Exposure | | |
Study	Is the case definition adequate	Represent-ativeness of the cases	Selection of controls	Definition of controls	Comparability of cases and controls on the basis of the design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-Response rate	Score
Yang and Zeng[14]	1	0	1	1	1	1	1	0	6
Enache et al[15]	1	0	1	1	2	1	1	0	7
Monte et al[16]	1	1	1	1	2	1	1	0	8
Huang et al[17]	1	0	1	1	1	1	1	0	6
Kovacs et al[18]	1	0	1	1	1	1	1	0	6
De Stefano et al[19]	1	0	1	1	2	1	1	0	7
Nakai et al[20]	1	1	1	1	1	1	1	0	7
Muraru et a[22]	1	0	1	1	1	1	1	0	6
Marisa et al[25]	1	0	1	1	2	1	1	0	7
Wong et al[25]	1	0	1	1	1	1	1	0	6

| | For cohort studies | | | | | | | | |
| | Selection | | | | Comparability | | Outcome | | |
Study	Represent-ativeness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	Score
Cong et al[13]	1	0	1	1	1	1	1	1	7
Vieira et al[21]	1	0	1	0	1	1	1	1	6
Li et al[23]	1	1	1	1	2	1	1	1	8

Table 3

Meta-regression (inverse variance weights, n=13).

Var	Coef.	Std. err.	z	P>|z|	95% Conf. interval
Year	0.0088323	0.0844891	0.10	.917	−0.1567633; 0.1744278
Etiology	0.9592992	0.259405	3.70	.000	0.4508747; 1.467724
District	1.208733	0.6348962	1.90	.057	−0.0356407; 2.453107
System	−.2979979	0.7056963	−0.42	.673	−1.681137; 1.085141
_cons	−21.00023	170.0905	−0.12	.902	−354.3715; 312.3711

Table 2. The included studies were of median to high quality. Thus, the pooled data from include studies were credible.

3.2. Meta-analysis

As the studies had high levels of statistical, clinical, and methodological heterogeneity ($I^2 = 82.4\%$, $P = .000$), a sensitivity analysis was performed to assess the effect of individual study on pooled values by omitting single study. The results of sensitivity analysis indicated that data from each individual study had no influence on pooled values. To investigate this heterogeneity, a meta-regression was conducted to determine whether any clinical variables were associated with the LV remodeling. There were abundant data to explore the effects of publication date, distinct, 3D system, study design, and pattern of LV remodeling. Of all of the parameters, the pattern of remodeling was the main source for heterogeneity ($P = .000$). The meta-regression analysis results were shown in Table 3.

The result of subgroup meta-analysis suggested that SpI in the patients with eccentric remodeling was significantly higher
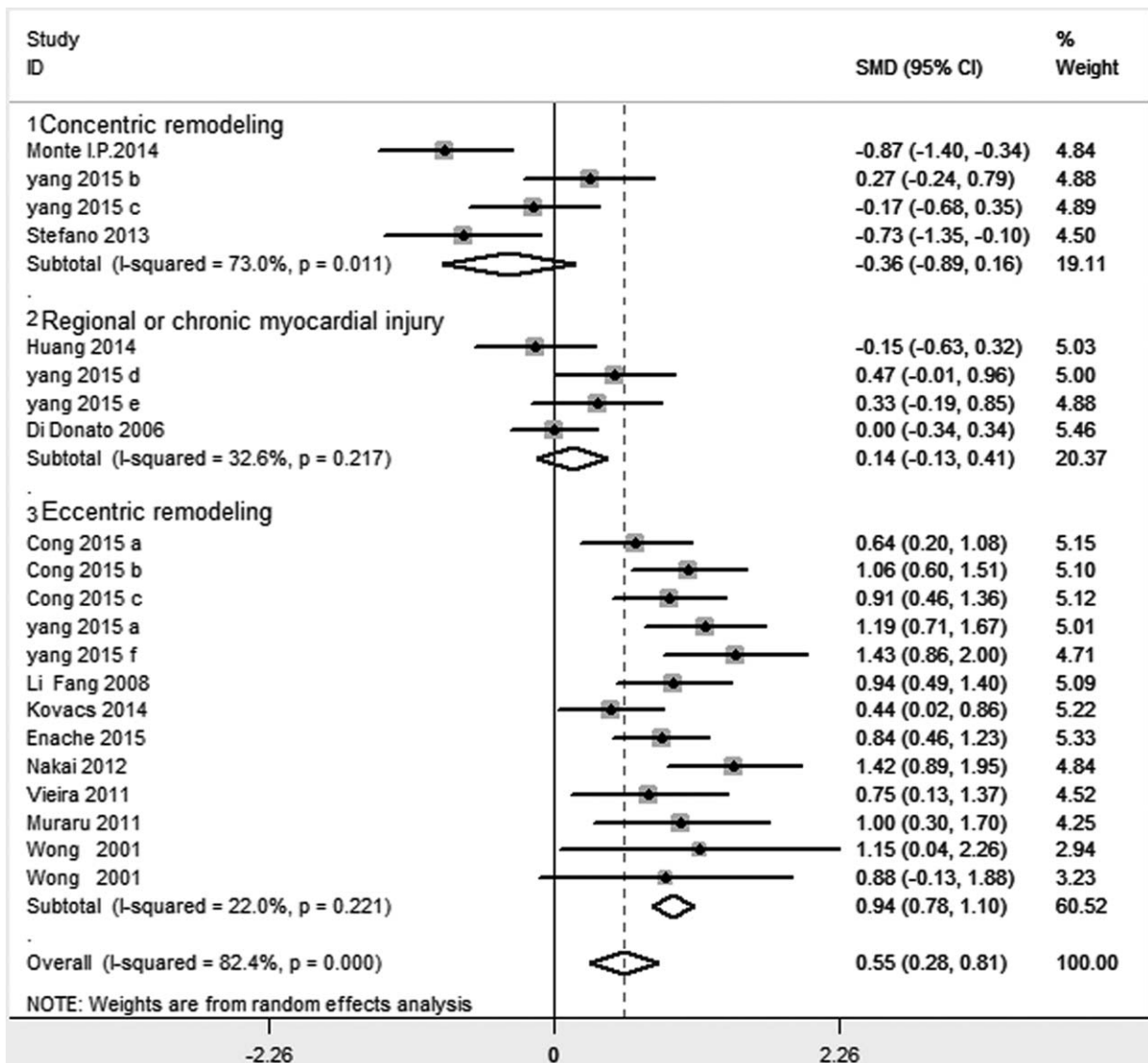

Figure 2. Forest plots of the difference of SpI between the patients with left ventricular remodeling and healthy controls and I^2 statistic for heterogeneity for the included studies. A subgroup analysis according to patterns of remodeling. CI = confidence interval, SMD = standard mean difference, SpI = sphericity index.
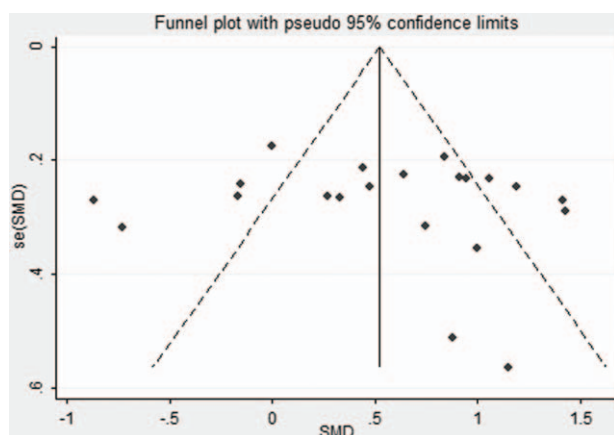
Figure 3. Funnel plots of publication bias for the differences in sphericity index between the patients with left ventricular remodeling and the healthy controls. SMD = standard mean difference.

compared with control group (95% CI, 0.78–1.10), whereas there was no statistic difference in LV SpI between healthy controls and patients with concentric hypertrophy (95% CI, −0.89 to 0.16) or myocardial injury (95% CI, −0.13 to 0.41) (Fig. 2).

3.3. Publication bias

Egger linear regression test and Funnel plot were performed to detect publication bias of included studies. The result of Egger test demonstrated that there was no significant evidence of publication bias ($t = 0.45$, $P = .66$). The shape of funnel plots did not show significant asymmetry (Fig. 3).

4. Discussion

Our findings suggested that 3D SpI can accurately reflect LV eccentric remodeling caused by volume overload or the entire LV dilation after MI, but cannot detect concentric hypertrophy in the early stage because of pressure overload or regional myocardial injury owing to AMI. LV remodeling occurs in response to a variety of physiological or pathological causes that are frequently intended to maintain cardiac homeostasis under changing myocardial loading conditions.[28] Physiological LV remodeling occurs in situations with underlying causes including exercise and pregnancy; pathological LV remodeling can occur as a result of hypertension, cardiomyopathy, valvular dysfunction, MI, cardiomyopathy, and connective tissue disease.[29] Despite the different etiologies of these diseases, LV remodeling shares common fundamental processes, which involve changes in molecule, cell, and myocardial tissue structure. As heart failure progresses, LV volume gradually leads to changes in ventricular shape and structure. Then the shape of LV becomes less conical or elongated and more spherical, and finally results in heart failure and even fatality if not attenuated or reversed by intervention. The capability of an early identification of the LV remodeling is vital for the aggressive pharmacological treatment. LV volume develops from an ellipse to more of a sphere after remodeling. 3D SpI as a novel parameter is capable of assessing geometric modification of the LV.

The classic view insists that concentric remodeling results in increased cardiomyocyte thickness but with little or no chamber dilation. The characteristics of this pattern are commonly

induced by pressure overload.[30] Increase in intraventricular pressure stimulates the ratio of LV wall thickness to chamber volume. An important finding from previous studies suggests that pressure-induced concentric hypertrophy might co-exist with both LV diastolic dysfunction and cavity dilation.[30] Thickened cardiomyocyte, cell apoptosis, and increased fibrous tissue can occur in concentric hypertrophy induced by pressure load. The increase of LV filling pressure exerts important effects on cardiac myocyte growth and phenotype, which ultimately leads to myocyte degeneration and loss. Early concentric hypertrophy gradually deteriorates into a dilated eccentric pattern.[31] Consequently, SpI may be normal, decreased, or increased. Eccentric remodeling/hypertrophy, which produces myocyte lengthening, is usually associated with increased volume and altered chamber configuration. The initial post-MI phase of LV remodeling comprises fibrotic repair of the infarctive region with scar formation, thinning of necrotic area, and local expansion.[28] Various strategies such as a biomechanically constrained filtering frame work have been developed to introduce a variety of physically meaningful constraints into myocardial motion analysis.[32] Wong et al[33] apply a biomechanical approach to detect the dysfunction of myocardial movement by cardiac images combined with biomechanical and computational techniques. As to regional expansion, LV conic index has been used to assess regional expansion in patients with AMI and has become more efficient in such assessment.[23] LV SpI represents the tendency of the real LV shape to become spherical during LV dilation, and thus cannot reflect regional expansion and identify dysfunction of myocardial movement. After this early stage, continued adverse remodeling develops into a pathological process associated with cardiac hypertrophy, chamber enlargement, and contractile dysfunction.[34] The shape of LV shifts from an elliptical to more of sphere, then the 3D SpI can accurately predict the changes in LV geometry in the subacute phase after acute MI. Another research indicates that LV SpI had no obvious change in patients with connective tissue disease if not complicated with chronic renal insufficiency or valvular disease.[17] This is principally because the SpI as a surrogate for fibers' orientation could not determine strain magnitude along different spatial directions, especially in the early phases of disease if LV geometry did not undergo apparent change.

Similar to other meta-analysis, this study has some limitations. The sample size is small. More studies, especially negative results are needed to better estimate the clinical value of 3D SpI in assessing LV remodeling. Although subgroup analysis was performed, the heterogeneity was still obvious. Also, studies included in this meta-analysis were mostly retrospective and the management of patients was not standardized, which may lead to clinical differences. Intraobserver and interobserver variability is inevitable in the measuring of LV SpI. Because we had no access to the original data from related studies, it would be difficult to accurately evaluate the patterns of LV remodeling. Therefore, the results in this meta-analysis are warranted to be verified in future research.

5. Conclusions

In conclusion, LV SpI represents the tendency of the real LV shape to become spherical during LV dilation, which can be used to assess the altered ventricular shape in patients with eccentric remodeling, but in the early stage, it cannot reflect regional expansion and identify dysfunction of myocardial movement in patients with regional or chronic myocardial injury. Besides, it

cannot reflect real LV shape accurately in different stages of concentric hypertrophy. Future studies are needed to determine whether SpI has a wider significance in evaluating the performance of LV in other patterns of remodeling.

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