MR-based Assessment of Myocardial 2D Strain using Feature Tracking: Association to Cardiovascular Risk Factors in a Population based Cohort free of Cardiovascular Disease

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ABSTRACT

Purpose: Myocardial strain analysis is a promising tool for the detection of subtle but relevant alterations of left ventricular function, also in asymptomatic subjects. Thus, we determined the feasibility of cardiac MR-based 2D global strain analysis using feature tracking and its association with cardiovascular risk factors in a sample from the general population.

Materials and Methods: Subjects without history of cardiocerebrovascular disease were enrolled in a sub-study of the population-based KORA (Cooperative Health Research in the Region of Augsburg) cohort. In all participants with absence of late gadolinium enhancement, longitudinal and circumferential global strain were measured on Cine SSFP imaging (TR: 29.97ms, TE: 1.46ms, ST: 8mm), using a semiautomatic segmentation algorithm (CVI42, Circle, Canada). Differences in strain values according to age, gender, BMI, hypertension, diabetes mellitus and hyperlipidemia were derived using linear regression analysis.

Results: Among 360 subjects (mean age, 56.2±9.2 years, 57% male), average global systolic radial strain was 40.1±8.2%, circumferential 19.9±2.7% and longitudinal 19.8±3.2%. Male gender was associated with decreased global strain values, independent of the strain direction (all $p<0.001$). While many cardiovascular risk factors were correlated with strain in univariate analysis, mainly waist-to-hip ratio and HbA1c remained associated with decreased radial and circumferential strain in fully adjusted models. Similarly, higher radial and circumferential strain was observed in older subjects ($\beta=0.14$, $p=0.01$ and $\beta=0.11$, $p=0.04$, respectively).

Conclusion: Strain analysis using MR feature tracking is feasible in population-based cohort studies and shows differences with respect to age and gender as well as an independent association with markers of metabolic syndrome.

Keywords:

Feature tracking, strain, cardiovascular magnetic resonance imaging, normal values, population-based cohort

ABBREVIATIONS

BMI	body mass index
CAD	coronary artery disease
ECG	Electrocardiography
EF	ejection fraction
HbA1c	glycated hemoglobin
HDL	high density lipoprotein
ICC	interclass correlation
LDL	low density lipoprotein
LV	left ventricular
MR	magnetic resonance
SD	standard deviation
SSFP	steady state free precision
WHR	waist-to-hip-ratio

INTRODUCTION

Cardiovascular disease remains as one of main burden of the general population in western countries [1]. While left ventricular (LV) dysfunction can have many different causes, e.g. fibrosis, inflammatory diseases or diabetes; its detection and quantification have significant impact on prognosis and treatment decisions [2, 3]. Traditionally, LV dysfunction was quantified using LV ejection fraction (EF). However, there is increasing evidence that LV ejection fraction only measures parts of the LV dysfunction and may not represent a good marker to determine early stages of LV dysfunction [4]. Thus, cardiac strain is a sensitive method to determine ventricle wall deformation and is an emerging parameter to characterize LV function.

The feature tracking algorithm was originally designed to analyze wall deformation for post-processing of echocardiographic studies, which is now adapted and applied to standard steady state free precision (SSFP) cine images as part of routine cardiac MR protocol. Mainly from echocardiographic data, it has been shown that strain is associated to age and gender [5], cardiovascular risk factors such as hypertension or diabetes [6, 7], and cardiac pathologies, such as dilative cardiomyopathy or fibrosis [3, 8]. Nevertheless up to now there are only three population based studies [9-11] which report on the incremental predictive value of tagged magnetic resonance imaging or echocardiography derived strain values for an incident heart failure and coronary artery disease. However, strain values based on cardiac MR analysis using feature tracking have not yet been measured in a population-based setting and knowledge on the impact of an individual risk factor in the entirety is limited.

Therefore, the aim of this study was to assess cardiac strain using cardiac MR feature tracking in a population-based cohort free of cardiovascular disease and to determine the independent association with cardiovascular risk factors.

METHODS

Study Population

The study population consisted of subjects recruited from the FF4 follow-up of the KORA (Cooperative Health Research in the Region of Augsburg) S4 study, a large population-based cohort study. The study design, sampling method and data collection are described in detail elsewhere [12].

Subjects were excluded in any case of contraindication of undergoing MRI, known allergy against gadolinium compounds, or serum creatinine ≥1.3 mg/dl. In addition, we excluded subjects with

- Ejection fraction < 55%
- presence of Late Gadolinium Enhancement (LGE)
- incomplete cardiac MR sequences

The study was approved by the institutional review board and all participants provided written informed consent.

Clinical assessment

Assessment regarding the presence of cardiovascular risk factors was performed as part of the standard follow-up of the main cohort study. Details are described in detail elsewhere [12] ; briefly, hypertension was defined as systolic blood pressure of at least 140 mmHg or diastolic blood pressure of at least 90 mmHg or current antihypertensive treatment. Subjects were classified as smokers if they had smoked at least one cigarette per day in the year prior to the study. Body mass index (BMI) was defined as weight (kilograms) divided by the height squared ($meters^2$).

MR Image Acquisition

Cardiac MR was performed on a clinical 3.0T MR-Scanner (Magnetom Skyra, Siemens Healthcare, Erlangen, Germany). Cine images were obtained using a breathhold balanced steady state free precession sequence (SSFP) with retrospective ECG gating in 4-chamber view and in contiguous short axis slices covering the whole ventricle with 25 phases per cardiac cycle. Sequence parameters were as follows: repetition time/echo time (TR/TE) 29.97/1.46ms, ST 8mm, gap 2mm, field of view (FOV 297x360), Matrix 240x160, flip angle (FA) 62°, voxel size 1.5x1.5mm². Late gadolinium enhancement sequences were acquired 10 minutes after administration of gadopentetate dimeglumine (20 mmol/kg, Gadovist, Bayer Healthcare, Berlin, Germany).

MR Image Analysis

All analyses were performed using dedicated post-processing software (cvi42, Circle Cardiovascular Imaging, Calgary, Canada), which included a strain analysis tool based on tissue tracking [13].

Strain analysis was performed along a semiautomatic-defined endocardial and epicardial border throughout the cardiac cycle on standard cine MR images and can be performed in about 1-2 minutes depending on the requirement of manual corrections of detected borders. Furthermore the same contouring used for LV volumetric analysis can be recycled for feature tracking. Long axis view was used for the assessment of longitudinal strain, while short axis cines were used to derive circumferential and radial strain. Long axis views were only part of the analysis if LV outflow tract was excluded. Papillary muscles were assigned to the ventricular lumen. After defining an anterior and posterior insertion point of the right ventricle, the software algorithm automatically tracks the LV deformation [14]. The following parameters were derived: (1) global peak systolic radial strain, (2)

longitudinal and (3) circumferential strain. To determine intra- and inter-observer variability, the measurements were repeated by the same observer with a week time gap as well as by a second, independent observer in a subgroup of 30 consecutive subjects. In addition, cardiac volumes and function were derived from Cine SSFP images using semi-automatically methods according to current guidelines [15]. Presence of late gadolinium enhancement was assessed by two experienced readers as described previously [12].

Statistical analysis

All measured strain values were transformed into absolute values before being included into any analysis. Continuous data were described by mean ± standard deviation and categorical data as percentages, if not other specified. Differences according gender were assessed by two-sample t-test or chi-square test. A test for trend was applied to detect strain differences among age groups. Inter-rater and intra-rater variabilities of strain measurements were investigated by Bland-Altman plots presenting mean relative differences (±1.96*SD) between two observers and two observations, respectively. In addition, intra-class-correlation (ICC) coefficients were calculated by two-way random-effects model.

The relation among strain parameters was characterized by Pearson's correlation coefficients and 10^{th} and 5^{th} percentiles were chosen to present normal reference values. Linear regression models were used to assess unadjusted, age and sex adjusted and multivariable adjusted associations between potential risk factors and strain parameters providing β-coefficients with 95% confidence intervals. Risk factor variables associated with any of the three strain parameters independently of age and sex were included in the multivariable model. Normal distribution of residuals was checked visually. In the multivariable model, β-coefficients were additionally standardized by z-transformation of all included variables to compare β-coefficients and 95% confidence intervals in forest plots.

A two-sided p-value < 0.05 was considered to indicate statistical significance. All analyses were conducted with Stata 14.1 (Stata Corporation, College Station, TX, U.S.A.).

RESULTS

A total of 379 subjects without past medical history of stroke, myocardial infarction or revascularization and absence of late gadolinium enhancement (n=11) were included in the analysis. Due to reduced image quality of the cardiac MR data (n=9) or incomplete cardiac MR sequences (n=10), 19 subjects were excluded from cardiac analysis (5%). Risk factor characteristics of the analysis cohort (n=360) are shown in **Table 1**. Briefly, the cohort consisted of middle-aged subjects (mean 56 years, range 39-73 years) with no significant differences with respect to gender (57% males). The MR imaging derived, basic LV parameters ranged within established normal values (**Table 1**).

Cardiac Strain Assessment using MR Feature Tracking

Assessment of radial and circumferential strain was feasible in all 360 subjects; longitudinal strain assessment was performed in 295 subjects, only, since the LV outflow tract was part of the 4-chamber-view in 65 subjects. The excluded subjects were more frequently male (p=0.03) and with higher BMI (p=0.004) but did not differ from the remaining cohort with respect to age, blood pressure, smoking, and diabetes (all $p \geq 0.08$).

Intra-rater reproducibility was good to excellent for all strain directions (ICC between 0.79 and 0.93) with low relative differences (**Appendix E1**). With respect to inter-reader reproducibility, ICC was only moderate (0.59) for radial while remaining good for longitudinal and circumferential strain (ICC 0.73 and 0.70, respectively; **Appendix E2**).

Cardiac Strain in a General Population

Average global systolic radial strain was 40.1±8.2%, circumferential strain 19.9±2.7% and longitudinal strain 19.8±3.2%.

Using 10yr-age-categories, no significant differences were observed across age for all strain directions (all p≥0.23; **Figure 1**), however, in linear regression analysis using age as a continuous measure, a slightly higher radial strain was observed in older subjects (β=0.10, p=0.04). Longitudinal and circumferential strain showed also no association with age in this univariate analysis (p=0.89 and 0.15, respectively).

In contrast, all strain measurements differed significantly with respect to gender (**Figure 2**), with female subjects always demonstrating higher strain values (21.0±2.9% vs. 18.9±3.1% for longitudinal, p<0.001; 43.5±7.5% vs. 37.5±7.8% for radial, p<0.001; and 21.1±2.3% vs. 19.0±2.6% for circumferential strain, p<0.001). Gender-specific percentiles (10^{th} and 5^{th}) as potential normal values are listed in **Appendix E3**.

Association of Cardiovascular Risk Factors with Strain Measurements

Beside gender, several cardiovascular risk factors were associated with strain measurements in univariate analysis; particular increased WHR, increased systolic/diastolic blood pressure, presence of diabetes mellitus, increased levels of HbA1c and triglycerides were associated with decreased strain values (**Table 2**), independent of the strain direction. Furthermore, increased levels of LDL were associated with decreased radial and circumferential strain besides increased BMI was associated with decreased circumferential strain (**Table 2**). Increased levels of HDL were positively associated with strain, independent of the strain direction (**Table 2**).

More importantly, the association of HbA1c, triglycerides, and HDL with strain persisted after adjustment for age and gender for all directions (**Table 3**), while diabetes remained only statistically significant associated with radial and circumferential strain (p=0.04 and 0.006, respectively) and LDL with radial strain (**Table 3**).

In fully adjusted models, male gender remained associated with decreased strain for all strain directions (all $p \leq 0.01$; **Figure 3**). Furthermore, WHR and HbA1c were independently associated with decreased radial and circumferential strain (**Figure 3**). In addition, increased diastolic blood pressure was associated with decreased longitudinal strain and age was positively associated with radial and circumferential strain in fully adjusted models (**Figure 3**). All other cardiovascular risk factors attenuated in the association to strain.

DISCUSSION

In this sample drawn from a general population without known or evidence of cardiovascular disease, MR imaging-based strain assessment using feature tracking is feasible and provides reproducible results. Our findings demonstrate that strain measurements differ significantly between gender and are independently associated with cardiovascular risk factors linked to metabolic disorders, which was less prominent for longitudinal strain than for the other strain directions.

Strain Measurement using Feature Tracking

Strain imaging is emerging since it may add information to traditional LV assessment and may provide insights into the underlying structure of myocardial dysfunction and therefore may allow for detection of subtle and early cardiac functional alterations. Feature tracking using SSFP images, which can be derived from a routine cardiac MR protocol, can overcome some disadvantages from other techniques, including angle dependency and time consuming additional sequences. This technique allows for reproducible quantification of strains on an intra- and inter-observer level, which is best on a global level [16]. In this present study, we also found the best inter-rater reproducibility for global peak systolic longitudinal strain followed by circumferential strain and then radial strain. The fact that radial strain, as opposed to circumferential strain, is derived from both endocardial and epicardial motion and therefore its quantification relies on the simultaneous tracking of both regions of interest may lead to the lower reproducibility. 3D strain analysis can detect variations in strain more precise as 2D strain assessment might miss changes in longitudinal strain values at the anterior and posterior wall as well as it takes in account the counter-directional helical arrangement of the myofibres. Referring to reproducibility we therefore

expect lower intra- and interrater-variability for 3D feature tracking. As our cmr protocol was part of a whole body MR protocol, we only acquired 4-chamber and short-axis views.

Association to Age, Gender and Cardiovascular Risk Factors

In contrast to recent published data from echocardiography we assessed the independent influence of a single cardiovascular risk factor in a sample from general population and not only one specific risk factor such as e.g. hypertension. The magnitude of global peak systolic strain is higher in women, which was independent of the strain direction and remained significant after adjustment for potential confounders. Thus, we confirm previous MR studies showing similar differences by using feature tracking as well as myocardial tagging [5, 17]. Using regression analysis, only radial strain showed a significant age-dependency in univariate and multivariate analysis; interestingly, this has also previously been demonstrated by others [5]. In addition, circumferential strain was negatively confounded and showed a positive association to age. These findings are in line with previous results from Taylor et al., describing a positive relation between circumferential but not longitudinal strain in middle aged individuals [17]. However, there is currently no clear consensus on the relationship between gender and age given that there are also several studies showing no [18] or inverse associations [19, 20].

Type-2 diabetes mellitus together with arterial hypertension, obesity, dyslipidemia and smoking is one of the most prevalent cardiovascular risk factor [21] and the most important risk factors of cardiac remodeling [22]. For example, Nakai et al [23] showed that patients with type-2 diabetes and normal LV ejection fraction had impaired LV longitudinal and circumferential strain compared with healthy controls. Our investigation demonstrated that global peak systolic strain values were also decreased in patients with diabetes; however, the association was stronger to HbA1c levels, which remained as an independent predictor.

Similarly, other studies showed also an association of HbA1c to diabetic comorbidities, in particular to cardiac dysfunction and remodeling [24].

Further independent association was observed for WHR, which is a marker for increased visceral adiposity. Severe obesity was previously associated with lower regional systolic strain [25] and Wong et al. [26] found that overweight or obese subjects without obvert heart disease had significantly lower long-axis strain values. But more importantly, in our study BMI was not associated while WHR did, this could indicate strain is associated with more metabolic active fat depots rather with overall obesity. In contrast, we found only in univariate analysis an inverse association between increasing levels of triglycerides for all strain directions as well as between increasing levels of LDL and circumferential and radial strain. These results are in line with previous studies in obese adults [27], but the attenuation of the associations in multivariate analysis may be explained by confounding of metabolic active fat depots.

With respects to hypertension, we observed lower strain levels in hypertensive subjects, nevertheless only diastolic blood pressure and longitudinal strain remained significantly associated in fully adjusted models. Previous studies reported also lower GLS in hypertensives [28, 29]. Further, Mizuguchi et al. demonstrated a decrease of peak systolic strain values in 3 directions in patients with concentric LV hypertrophy, as present in long-lasting hypertension, compared to the control group [30].

Strain calculating using Cine SSFP images as part of the cardiac routine protocol can easily add a potential clinical value in early detection of cardiomyopathies, for example due to diabetes or medication.

Limitations

The presented results need to be evaluated in the context of their limitations. Our analyses are based on global peak systolic strain measurement and do not include segmental analysis given the fact that global peak systolic strain analysis is preferable in clinical routine due to its higher reproducibility. Yet, global values might not fully reflect subtle changes of wall motion abnormalities. Furthermore, we only used 2D strain assessment, which might miss changes in longitudinal strain values at the anterior and posterior wall and does not reflect the complex counter-helical arrangement of myocardial fibers. Compared to 2D echocardiography the temporal resolution is lower in CMR Imaging. Therefore calculation of peak systolic strain values can be affected and are not interchangeable between the methods. Furthermore, our subjects were relatively healthy and had only minor cardiac alterations, thus known observations from diseased, clinical cohorts may not be reproduced. However, this particular cohort of subjects without known cardiovascular disease drawn from a general population is of high interest for prevention medicine.

CONCLUSION

Strain analysis using 2D MR feature tracking shows in a cohort free of cardiocerebrovascular disease beside differences with respect to gender an independent association of global peak systolic strain and risk factors pertaining to metabolic syndrome, such as glycated hemoglobin or waist-to-hip ratio. However all other cardiovascular risk factors need to be considered while talking about normal values as they show an univariate association.

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FIGURES AND LEGENDS

Figure 1: Global Peak Systolic Strain by Age

Differences among 10-years age groups displayed by violin plots providing information for median, interquartile range, upper- and lower-adjacent values and value distributions estimated by kernel density; no statistical significant difference was obtained across age-categories for all strain directions using a trend test.

Figure 2: Global Peak Systolic Strain by Gender

Differences among gender displayed by violin plots providing information for median, interquartile range, upper- and lower-adjacent values and value distributions estimated by kernel density; women had significantly higher strain values independent of strain direction.

Figure 3: Forrest Plot for the Independent Association of Demographics with Longitudinal, Radial and Circumferential Strain

APPENDIX

E1: Bland-Altman-Plots for Intra-Reader Reproducibility.

Relative difference between observation 1 and observation 2 for measurements of longitudinal, radial, and circumferential strain (mean=solid line; ±1.96*SD=dashed line).

E2: Bland-Altman-Plots for Inter-Reader Reproducibility.

Relative difference between observer 1 and observer 2 for measurements of longitudinal, radial, and circumferential strain (mean=solid line; ±1.96*SD=dashed line).

E3: Gender-specific 10^{th} and 5^{th} Percentile as Reference Values in a General Population without known or evident cardiocerebrovascular disease.

Supporting Figure 1:

Determination of Global Longitudinal Strain:

a) Cine SSFP 4-chamber view with semiautomatic contouring of endocardium (red) and epicardium (green). The blue lines are marking the mitral valve plane and the extension of left ventricle.

b) Global Longitudinal Strain curve of a 51year old female with a peak systolic value of -25%

Supporting Figure 2:

Determination of global radial and circumferential strain in a 40year old male

(a) midventricular Cine SSFP short axis view with semiautomatic contouring of endocardium (red) and epicardium (green). Papillary muscles are marked in pink. Detection of radial strain, as opposed to circumferential strain, is derived from both endocardial and epicardial motion.

Strain curves of this study participant with a global peak radial strain (b) of +44% and peak global circumferential strain (c) of -22%.

Supporting Figure 3:

Determination of global radial and circumferential strain in a 52year old male

(a) mid-ventricular Cine SSFP short axis view with semiautomatic contouring of endocardium (red) and epicardium (green). Papillary muscles are marked in pink. Detection of radial strain, as opposed to circumferential strain, is derived from both endocardial and epicardial motion.

Strain curves of this study participant with a global peak radial strain (b) of +30% and a peak global circumferential strain (c) of -18%.