Left ventricular longitudinal systolic function analysed by 2D speckle-tracking echocardiography in heart failure with preserved ejection fraction: a meta-analysis

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ABSTRACT

Background The purpose of this meta-analysis was to confirm if the global longitudinal systolic function of the left ventricle (LV) is altered in patients with heart failure with preserved ejection fraction (HFrEF).

Methods We searched in different databases (Medline, Embase and Cochrane) studies that analysed LV global longitudinal systolic strain (GLS) in patients with HFrEF and in controls (such as healthy subjects or asymptomatic patients with arterial hypertension, diabetes mellitus or coronary artery disease).

Results Twenty-two studies (2284 patients with HFrEF and 2302 controls) were included in the final analysis. Patients with HFrEF had significantly lower GLS than healthy subjects (mean −15.7% (range −12% to −18.9%) vs mean −19.9% (range −17.1% to −21.5%), weighted mean difference −4.2% (95% CI −3.3% to −5.0%), p < 0.001, respectively). In addition, patients with HFrEF had also significantly lower GLS than asymptomatic patients (mean −15.5% (range −13.4% to −18.4%) vs mean −18.3% (range −15.1% to −20.4%), weighted mean difference −2.8% (95% CI −1.9% to −3.6%), p < 0.001, respectively). In line, 10 studies showed that the rate of abnormal GLS was significantly higher in patients with HFrEF (mean 65.4% (range 37%−95%)) than in asymptomatic subjects (mean 13% (range 0%−29.6%).

Regarding the prognostic relevance of abnormal GLS in HFrEF, two multicentre studies with large sample size (447 and 348) and high number of events (115 and 177) showed that patients with abnormal GLS had worse cardiovascular (CV) outcomes than those with normal GLS (HR for CV mortality and HF hospitalisation 2.14 (95% CI 1.26 to 3.66) and 1.94 (95% CI 1.22 to 3.07)), even adjusting these analyses for multiples clinical and echocardiographic variables.

Conclusion The present meta-analysis analysing 2284 patients with HFrEF and 2302 controls confirms that the longitudinal systolic function of the LV is significantly altered in high proportion of patients with HFrEF. Further large multicentre studies with the aim to confirm the prognostic role of abnormal GLS in HFrEF are warranted.

INTRODUCTION

Heart failure with preserved ejection fraction (HFrEF) has long been considered a disorder characterised principally by left ventricular (LV) diastolic alterations. While it is correct, recent studies using two-dimensional speckle-tracking echocardiography (2DSTE) have suggested that the longitudinal systolic function of the LV is altered in HFrEF. Nonetheless, despite these interesting pathophysiological insights, other studies including old control patients and well-characterised patients with HFrEF did not find any difference in LV global longitudinal systolic strain (GLS) between HFrEF and controls as well as any clinical relevance of GLS in HFrEF. Accordingly, given these contradictory results, at this time it is difficult to confirm the magnitude of an altered LV longitudinal systolic function in patients with HFrEF.

In addition, it remains uncertain the exact rate of abnormal GLS in HFrEF or whether the prevalence of this LV systolic alteration is significantly different to asymptomatic controls. In line, a global examination or meta-analysis addressing all these important issues in HFrEF is lacking.

Therefore, the purpose of this meta-analysis was to analyse the global longitudinal systolic function of the LV in all published studies that included HFrEF and control patients with the aim to confirm if the global longitudinal systolic function of the LV is altered in patients with HFrEF.

METHODS

Search process

We searched in different databases (Medline, Embase and Cochrane) published studies...
KEY QUESTIONS

What is already known about this subject?

► Heart failure with preserved ejection fraction (HFpEF) has long been considered a disorder characterised principally by left ventricular (LV) diastolic alterations. While it is correct, recent studies using two-dimensional speckle-tracking echocardiography have suggested that the longitudinal systolic function of the LV is altered in HFpEF. Nonetheless, despite these interesting pathophysiological insights, other studies including old control patients and well-characterised patients with HFpEF did not find any significant difference in LV global longitudinal systolic strain (GLS) between HFpEF and controls. Accordingly, given these contradictory results, at this time it is difficult to confirm the magnitude of an altered LV longitudinal systolic function in patients with HFpEF. In addition, it remains uncertain the exact rate of abnormal GLS in HFpEF or whether the prevalence of this LV systolic alteration is significantly different to asymptomatic controls. In line, a global examination or meta-analysis addressing all these important issues in HFpEF is lacking.

What does this study add?

► On the basis of 22 studies, 2284 patients with HFpEF and 2302 controls, the findings of this meta-analysis confirm that patients with HFpEF have significantly lower LV longitudinal systolic function than asymptomatic controls and that a longitudinal systolic dysfunction of the LV is common among patients with HFpEF.

How might this impact on clinical practice?

► Several clinical trials have been conducted to restore the diastolic function of the LV in patients with HFpEF with the aim to improve the prognosis of these patients. However, none of these treatments has been shown to decrease mortality in patients with HFpEF. For this reason, additional pathophysiological mechanisms should be taken into consideration in the design of new clinical trials in this heterogeneous disease. The present meta-analysis analysing 2284 patients with HFpEF and 2302 controls confirms that the longitudinal systolic function of the LV is significantly altered in high proportion of patients with HFpEF. In addition, two large multicentre studies showed that an abnormal LV longitudinal systolic function is significantly linked to cardiovascular mortality and HF hospitalisation in these patients. Therefore, we consider that further large multicentre studies with the aim to validate the prognostic relevance of an abnormal GLS in patients with HFpEF are warranted, because if the prognostic role of this LV systolic alteration is confirmed, a future therapeutic target could arise on this complex disease, for which, so far, no effective therapies exist.

RESULTS

Study population

We identified 953 potential studies from published literature (see figure 1). Twenty-nine studies met the eligibility criteria analysing the different databases (Medline, Embase and Cochrane) (see table 1). Twenty-two studies had a control group (2284 patients with HFpEF and 2302 controls) and nine studies had follow-up with outcomes analyses (1847 patients with HFpEF) (see table 1).

Selection criteria

The criteria to include the studies were: (1) patients with diagnosis of HFpEF using a cut-off of left ventricular ejection fraction (LVEF) ≥ 45%; (2) available LV GLS analysed by 2DSTE at rest in at least 12 LV segments and (3) available control group or data regarding the prevalence of abnormal GLS or data regarding the prognosis of GLS. Control group in the analysis was defined as healthy subjects or as asymptomatic patients with some cardiovascular (CV) risk factor or disease such as arterial hypertension, diabetes mellitus or history of coronary artery disease (CAD). Furthermore, in order to avoid analysing twice the same population, we selected only one study when the same population was included in two or more HFpEF studies for the same research group.

Data abstraction and variable definition

Data were independently extracted by two reviewers (DAM and X-XM). Clinical characteristics, design, imaging modalities for quantification of GLS, baseline values of GLS in HFpEF and controls, rate of abnormal GLS and hazard ratio (HR) or odds ratio (OR) that linked GLS to CV outcomes were extracted from each study. The key variable under study was GLS (ie, peak systolic LV strain) derived from the myocardial analysis of the LV in longitudinal direction in the apical 4-chamber, 2-chamber and 3-chamber views (ie, ≥12 LV segments) and using 2DSTE at rest.

Statistical analysis

We used Review Manager (V.5.3, Cochrane) to analyse the data. All analyses were in accordance with the PRISMA-IPD Statement recommendations. Mean, 95% confidence interval (CI) and range were calculated for each variable from all studies. In line, we determined the weighted mean difference (WMD) for each variable in each study. A fixed model was used to obtain WMD. Statistical heterogeneity in GLS values among studies was evaluated using the I² statistics. In addition, we performed a meta-regression analysis in order to detect the possible sources of statistical heterogeneity on GLS values in the study population. Moreover, a sensitivity analysis was performed in order to decrease the possible bias or sources of statistical heterogeneity on GLS. In this regard, we performed subgroup analyses including studies with ≥ 100 patients with HFpEF and studies with < 100 patients with HFpEF as well as studies with patients with HFpEF without atrial fibrillation. Furthermore, with the purpose of evaluating the association of GLS with CV outcomes in HFpEF, we analysed the link of GLS to CV outcomes analysing the OR and HR in logistic and Cox regression analysis in the studies. Differences were considered statistically significant when p value was < 0.05.
Concerning the clinical and LV characteristics of the study population, there were differences between HFpEF and controls regarding comorbidities such as arterial hypertension, diabetes mellitus and history of CAD and regarding LV characteristics such as LV mass and LV filling pressures (table 2). Nonetheless, in a meta-regression analysis, the severity of LV filling pressures was the main factor linked to GLS in patients with HFpEF (see table 3).

**LV longitudinal systolic function in HFpEF versus controls**

Patients with HFpEF had significantly lower GLS than control subjects (see table 2 and figures 2 and 3). These differences in GLS between HFpEF and controls were significant between patients with HFpEF and asymptomatic patients (figure 2) as well as between patients with HFpEF and healthy subjects (figure 3). In line, 19 out of 22 studies showed that patients with HFpEF had significantly lower values of GLS than controls (see figures 2 and 3). On the other hand, there were minimal differences in LVEF between patients with HFpEF and controls and the mean range of LVEF in HFpEF and controls was within the normal range for LVEF (ie, 55%–75%) (see table 2 and figure 4).

In a statistical variability analysis ($\Gamma^2$), a statistical heterogeneity in GLS values among studies was found (see figures 2 and 3). In this regard, in order to detect the possible sources of statistical heterogeneity on GLS values in the study population, a meta-regression and sensitivity
| Study                  | Number of patients with HFpEF | Age (years) | Women | LVEF criteria | LV strain (GLS) | Control group | Follow-up |
|-----------------------|-------------------------------|-------------|-------|---------------|----------------|---------------|-----------|
| Wang et al^a          | 20                            | 63 ± 16     | 35%   | ≥ 50%         | 18 LV segments - EchoPac | yes           | no        |
| Liu et al^b           | 26                            | 68 ± 13     | 31%   | ≥ 50%         | 18 LV segments - EchoPac | yes           | no        |
| Phan et al^c          | 40                            | 67 ± 10     | 73%   | ≥ 50%         | 12 LV segments - EchoPac | yes           | no        |
| Tan et al^d           | 56                            | 72 ± 7      | 68.6% | > 50%         | 12 LV segments - EchoPac | yes           | no        |
| Kuo et al^e           | 21                            | 70 ± 10     | 44%   | > 50%         | 18 LV segments - EchoPac | yes           | no        |
| Morris et al^f        | 119                           | 74 ± 12     | 64%   | > 50%         | 18 LV segments - EchoPac | yes           | no        |
| Vip et al^g           | 122                           | 65 ± 12     | 30%   | > 50%         | 18 LV segments - EchoPac | yes           | no        |
| Age et al^h           | 10                            | 76 ± 13     | 65%   | > 50%         | 18 LV segments - EchoPac | yes           | no        |
| Obokata et al^i       | 40                            | 76 ± 10     | 45%   | ≥ 50%         | 12 LV segments - EchoPac | yes           | no        |
| Kolli et al^j         | 21                            | 70 ± 13     | 77%   | ≥ 50%         | 18 LV segments - EchoPac | yes           | no        |
| Merit et al^k         | 40                            | 70 ± 10     | 40%   | > 50%         | 18 LV segments - EchoPac | yes           | no        |
| Loo et al^l           | 58                            | 76 ± 9      | 51.9% | > 50%         | 18 LV segments - EchoPac | yes           | no        |
| Wang et al^m          | 359                           | 66 ± 8      | 37%   | > 50%         | 18 LV segments - EchoPac | yes           | no        |
| Donal et al^n         | 25                             | 64 ± 1      | 78%   | 50%           | 18 LV segments - EchoPac | yes           | no        |
| Sniitt et al^o        | 401                          | 68 ± 13     | 75%   | 50%           | 18 LV segments - EchoPac | yes           | no        |
| Kono et al^p          | 217                           | 76 ± 13     | 63%   | > 50%         | 18 LV segments - EchoPac | yes           | no        |
| Toulani et al^q       | 228                           | 72 ± 10.5   | 63.8% | > 50%         | 18 LV segments - EchoPac | yes           | no        |
| Maiso et al^r         | 46                            | 65 ± 13     | 45%   | > 50%         | 18 LV segments - EchoPac | yes           | no        |
| Oka et al^s           | 58                            | 75 ± 8      | 52%   | > 50%         | 18 LV segments - EchoPac | yes           | no        |
| Ito et al^t           | 102                           | 69 ± 11     | 57%   | > 50%         | 18 LV segments - EchoPac | yes           | no        |
| Dova et al^u          | 129                           | 75 ± 11     | 54%   | > 50%         | 18 LV segments - EchoPac | yes           | no        |
| Hong et al^v          | 139                           | 73 ± 11.5   | 52%   | 50%           | 18 LV segments - EchoPac | yes           | no        |
| Loo et al^w           | 142                           | 73 ± 11.5   | 54%   | > 50%         | 18 LV segments - EchoPac | yes           | no        |
| Bosch et al^x         | 139                           | 62 ± 11     | 52%   | > 50%         | 18 LV segments - EchoPac | yes           | no        |

In the study by Bosch et al., 159 out of 219 patients were feasible to perform GLS analyses and the reported follow-up with outcomes analysis did not include GLS. The studies by Donal et al. includes a first outcomes analysis on GLS using a continuous Cox regression analysis and a second post-hoc outcomes analysis on GLS using a dichotomous Cox regression analysis.

GLS, global longitudinal systolic strain; HFpEF, heart failure with preserved ejection fraction; LV, left ventricular; LVEF, left ventricular ejection fraction.

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Meta-analysis was performed. In effect, we found that the severity of LV filling pressures (measured by the mitral average septal-lateral E/e’ ratio) was the main factor linked to heterogeneity on GLS values among HFpEF studies, whereas the sample size, age and the presence of AF were not significantly linked to GLS (see table 3). In addition, with the purpose of ruling out the possible role of the sample size on GLS values, we performed a

Table 2  Global clinical and echocardiographic characteristics of studies with patients with HFpEF and control subjects

| Clinical and cardiac factors | Patients with HFpEF (n=2284) | Asymptomatic patients (n=1647) | Healthy subjects (n=655) |
|-----------------------------|-------------------------------|-------------------------------|-------------------------|
| Age, years                  | 68.5 (51–78)                 | 64.7 (47–78)                 | 55 (36.5–70)            |
| Women                       | 55.2% (30%–77%)              | 50.9% (32.4%–77%)            | 58.7% (40%–70.5%)       |
| Arterial hypertension       | 82% (40%–100%)               | 70.3% (8%–100%)              | 0%                      |
| Diabetes mellitus           | 33.4% (5%–60%)               | 20.8% (0%–43%)               | 0%                      |
| Obesity                     | 37.8% (29.4%–58.7%)          | 10.8% (8%–16.2%)             | 0%                      |
| History of CAD              | 31.7% (0%–91.3%)             | 13.6% (0%–33%)               | 0%                      |
| Atrial fibrillation         | 8.6% (0%–73%)                | 0.1% (0%–1%)                 | 0%                      |
| Echocardiographic characteristics |                           |                               |                         |
| LV longitudinal systolic strain, % | −15.5 (−12 to −18.9)  | −18.3 (−15.1 to −20.4)      | −19.9 (−17.1 to −21.5)  |
| LV ejection fraction, %     | 61.9 (58–72)                 | 64 (56–71)                   | 63.4 (60–67.6)          |
| LV mass index, g/m²         | 105.7 (54–144)               | 85.7 (49–115)                | 78.8 (72.7–85)          |
| LA volume index, mL/m²      | 37.7 (24.8–55)               | 26.9 (16–38)                 | 25.4 (18–44)            |
| Mitral septal-lateral e’, cm/s | 5.9 (3.4–8)                | 7.5 (4.8–12)                 | 11.1 (9–13.5)           |
| Mitral septal-lateral E/e’ ratio | 14.9 (10.2–19.9)       | 10 (6.8–12.6)                | 7.3 (6.3–8.5)           |

Data are expressed as mean and (range) (ie, the mean value of each variable from all studies as well as the range of the means from all studies). GLS (ie, average longitudinal peak systolic strain from ≥12 LV segments).

CAD, coronary artery disease; GLS, global longitudinal systolic strain; HFpEF, heart failure with preserved ejection fraction; e’, septal and lateral annular mitral early diastolic peak velocity using pulsed-TDI; E, mitral inflow early diastolic peak velocity using pulsed Doppler; LA, left atrial.

Table 3  Clinical and cardiac factors linked to LV global longitudinal systolic strain (GLS) in patients with HFpEF - Meta-regression analysis

| Clinical and cardiac factors | GLS, % | β (95% CI) | p Value |
|-----------------------------|--------|------------|---------|
| Age, per 1 year             | −0.05  | −0.15 to 0.05 | 0.32    |
| Prevalence of women, per 1% | 0.08   | −0.04 to 0.12 | < 0.01  |
| Prevalence of arterial hypertension, per 1% | 0.02 | −0.03 to 0.07 | 0.41    |
| Prevalence of diabetes, per 1% | −0.02 | −0.08 to 0.02 | 0.31    |
| Prevalence of CAD, per 1%   | −0.04  | −0.01 to 0.07 | < 0.01  |
| Prevalence of AF, per 1%    | −0.02  | −0.06 to 0.01 | 0.27    |
| LVEF, per 1%                | 0.29   | 0.04 to 0.53  | 0.03    |
| LV mass, per 1 g/m²         | −0.03  | −0.01 to 0.06 | 0.05    |
| Mitral septal-lateral e’, per 1 cm/s | 0.34 | −0.40 to 1.08 | 0.38    |
| Mitral septal-lateral E/e’, per 1 unit | −0.39 | −0.17 to 0.61 | < 0.01  |
| Sample size of the study, per one patient | 0.01 | −0.01 to 0.02 | 0.53    |

The meta-regression analysis was performed in all studies as shown in figures 2 and 3. GLS (ie, average longitudinal peak systolic strain from ≥12 LV segments). The β coefficient indicates the estimated change in GLS for every estimated change in the independent variable analysed.

AF, atrial fibrillation; CAD, coronary artery disease; GLS, global longitudinal systolic strain; HFpEF, heart failure with preserved ejection fraction; e’, septal and lateral annular mitral early diastolic peak velocity using pulsed-TDI; E, mitral inflow early diastolic peak velocity using pulsed Doppler; β, beta coefficient; LV, left ventricular; LVEF, left ventricular ejection fraction.
subgroup analysis including studies with ≥ 100 and < 100 patients with HFrEF. In this respect, we found that patients with HFrEF had significantly lower values of GLS than controls in studies that included both ≥ 100 and < 100 patients with HFrEF (see figures 5 and 6). In addition, in order to exclude the role of AF on the statistical heterogeneity of GLS, we performed a subgroup analysis including only those studies that included patients with HFrEF without AF. In this regard, we found that patients with HFrEF without AF had also significantly lower values of GLS than controls (see figure 7).

Prevalence of LV longitudinal systolic dysfunction in HFrEF

Regarding the prevalence of LV longitudinal systolic dysfunction in HFrEF, 10 studies (1810 patients with HFrEF and 462 asymptomatic controls) showed that the rate of abnormal GLS was significantly high in patients with HFrEF (mean 65.4% (range 37%-95%)), whereas in asymptomatic subjects was only of 13% (range 0%-29.6%) (table 4). Nonetheless, only one study analysed the clinical and cardiac characteristics of patients with HFrEF with abnormal GLS.33

Prognostic relevance of LV longitudinal systolic dysfunction in patients with HFrEF

Nine studies analysed the prognostic relevance of GLS in patients with HFrEF (n=1847 patients with HFrEF; n of events=620) (see table 5). Four studies showed that GLS was associated with worse CV prognosis, but other five studies did not find any significant association of GLS with outcomes in patients with HFrEF (table 5). Six out of these nine studies analysed the association of GLS with outcomes using only continuous logistic or Cox regression analyses, whereas only three out of these nine studies analysed in a dichotomous analysis the link (ie, OR or HR) of an abnormal GLS to CV outcomes (table 5). Nonetheless, two out of these three studies were multicentre, with large sample size (447 and 348) and high number of events (115 and 177), and showed a significant association of an abnormal GLS with CV outcomes (HR for CV mortality and HF hospitalisation 2.14 (95% CI 1.26 to 3.66) and 1.94 (95% CI 1.22 to 3.07)) (see table 5).

Discussion

In the present study performing a meta-analysis regarding the longitudinal systolic function of the LV analysed by...
2DSTE in HFP EF, patients with HFP EF had significantly lower GLS than control subjects and an abnormal GLS was common among patients with HFP EF. Moreover, two large multicentre studies analysing the association of an abnormal GLS with CV outcomes found that an abnormal GLS was significantly linked to CV mortality and HF hospitalisation.

Main findings of this meta-analysis
On the basis of 22 studies, 2284 patients with HFP EF and 2302 controls, the findings of this meta-analysis confirm that patients with HFP EF have significantly lower LV longitudinal systolic function than asymptomatic controls and that a longitudinal systolic dysfunction of the LV is

Figure 4 Left ventricular ejection fraction (LVEF) in patients with heart failure with preserved ejection fraction (HFP EF) vs asymptomatic and healthy controls. The study by Shah et al\textsuperscript{15} was not included in this analysis because the value of LVEF in the control group was not reported.

Figure 5 LV global longitudinal systolic strain (GLS) in patients with heart failure with preserved ejection fraction (HFP EF) vs asymptomatic and healthy controls in studies including ≥ 100 patients with HFP EF. GLS is shown in absolute values.

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**Figure 4** Left ventricular ejection fraction (LVEF) in patients with heart failure with preserved ejection fraction (HFP EF) vs asymptomatic and healthy controls. The study by Shah et al\textsuperscript{15} was not included in this analysis because the value of LVEF in the control group was not reported.

**Figure 5** LV global longitudinal systolic strain (GLS) in patients with heart failure with preserved ejection fraction (HFP EF) vs asymptomatic and healthy controls in studies including ≥ 100 patients with HFP EF. GLS is shown in absolute values.
common among patients with HFpEF. Nonetheless, despite the fact that the number of studies and patients was large, the amount of studies reporting the characteristics of patients with abnormal GLS as well as the prognostic consequences of an abnormal GLS was lower. In fact, only one study analysed the clinical and cardiac characteristics of patients with HFpEF with abnormal GLS and only two large multicentre studies analysed in a dichotomous analysis the association of an abnormal GLS with CV outcomes.\textsuperscript{15 20 33} Accordingly, on the basis of this meta-analysis, we can confirm that the longitudinal systolic function of the LV is altered in high proportion of patients with HFpEF, but the clinical and cardiac characteristics of this subgroup of patients as well as the clinical consequences of LV longitudinal systolic dysfunction in patients with HFpEF need to be confirmed.

While nine studies have analysed the association of the longitudinal systolic function of the LV (analysed by GLS) with CV outcomes in patients with HFpEF,\textsuperscript{14 15 20 24 29–33} only two of these studies were multicentric, enrolled large number of patients (>500) and had high number of events (>100).\textsuperscript{15 20} In this regard, Shah \textit{et al}\textsuperscript{15} analysing the echocardiographic data of the TOPCAT trial found that an abnormal GLS was significantly linked to worse CV outcomes (CV death and HF hospitalisation) in patients with HFpEF. In agreement, Donal \textit{et al}\textsuperscript{20} analysing the echocardiographic data of the KaRen study found a significant association of an abnormal GLS with CV outcomes. However, other two smaller multicentre studies and three single-centre studies did not find any significant association of GLS with outcomes in HFpEF.\textsuperscript{29–33} Nonetheless, it is important to highlight that the analyses in the TOPCAT and KaRen studies were dichotomous analyses (ie, analysing the HR of an abnormal GLS with CV outcomes),\textsuperscript{15 20} whereas the other smaller studies analysed the association of GLS with CV outcomes using only continuous logistic or Cox regression analyses.\textsuperscript{29–33} Accordingly, while it is not possible to confirm in this meta-analysis if an abnormal GLS is linked to worse CV outcomes in HFpEF, we consider that further large multicentre studies with the aim to confirm the prognostic role of abnormal GLS in HFpEF are warranted.
**Figure 7**  LV global longitudinal systolic strain (GLS) in patients with HFpEF without atrial fibrillation vs asymptomatic and healthy controls. GLS is shown in absolute values.

**Table 4** Prevalence of LV longitudinal systolic dysfunction in patients with HFpEF vs controls

| Study            | HFpEF patients rate of abnormal GLS | Asymptomatic controls rate of abnormal GLS | Cut-off of abnormal GLS | LV segments analysed | Software package |
|------------------|------------------------------------|------------------------------------------|-------------------------|---------------------|-------------------|
| Wang et al       | 95%                                | 5%                                       | −16%                    | 18                  | EchoPac           |
| Liu et al        | 85%                                | 15%                                      | −17.5%                  | 18                  | EchoPac           |
| Morris et al     | 81.5%                              | 15.5%                                    | −16%                    | 18                  | EchoPac           |
| Yip et al        | 37%                                | 0%                                       | −16%                    | 18                  | EchoPac           |
| Kraigher-Krainer et al1 | 54.3%                  | 29.6%                                   | −15.8%                  | 12                  | TomTec            |
| Donal et al      | 39%                                | No control group                        | −16%                    | 18                  | EchoPac           |
| Shah et al       | 52%                                | Not reported                             | −15.8%                  | 12                  | TomTec            |
| Freed et al      | 75%                                | No control group                        | −20%                    | 12                  | TomTec            |
| DeVore et al     | 65%                                | No control group                        | −16%                    | 18                  | TomTec            |
| Huang et al      | 75.9%                              | No control group                        | −15.8%                  | 18                  | EchoPac           |

The rate of abnormal GLS indicates the prevalence of LV longitudinal systolic dysfunction. GLS (ie, average longitudinal peak systolic strain from ≥12 LV segments).

HFpEF, heart failure with preserved ejection fraction; GLS, global longitudinal systolic strain.
Table 5  Association of LV global longitudinal systolic strain (GLS) with outcomes in HFpEF

| Study          | Primary end point                  | Events (n) | Dichotomous univariate analysis Abnormal GLS HR (95% CI) | Dichotomous multivariate analysis Abnormal GLS HR (95% CI) | Continuous univariate analysis GLS 1SD or 1% decrease HR (95% CI) | Continuous multivariate analysis GLS 1SD or 1% decrease HR (95% CI) |
|----------------|-----------------------------------|------------|----------------------------------------------------------|----------------------------------------------------------|----------------------------------------------------------------|----------------------------------------------------------------|
| Shah et al15   | CV death or aborted cardiac arrest or HF hospitalisation | 115        | 2.26 (1.53 to 3.34)                                       | 2.14 (1.26 to 3.66)                                       | 1.13 (1.08 to 1.19)                                                | 1.14 (1.04 to 1.24)                                                |
| Donal et al19, 20* | All-cause death or HF hospitalisation | 177        | not reported                                             | 1.94 (1.22 to 3.07)                                       | not reported                                                      | not reported                                                      |
| Huang et al24  | All-cause death                     | 27         | 3.4 (1.02 to 11.3)                                       | 4.72 (1.25 to 17.8)                                       | not reported                                                      | not reported                                                      |
| Pellicori et al29 | CV death or HF hospitalisation      | 62         | not reported                                             | not reported                                             | 1.09 (1.00 to 1.19)                                                | 0.99 (0.90 to 1.11)                                                |
| Freed et al31  | All-cause death or CV hospitalisation | 115        | not reported                                             | not reported                                             | 1.25 (1.03 to 1.52)                                                | 1.17 (0.95 to 1.43)                                                |
| Obokata et al32 | CV death, non-fatal MI and HF exacerbation | 29         | not reported                                             | not reported                                             | 0.99 (0.87 to 1.13)                                                | not reported                                                      |
| Stampehl et al14† | CV death or HF hospitalisation    | 17         | not reported                                             | not reported                                             | not reported                                                      | not reported                                                      |
| Wang et al30, ‡ | All-cause death or HF hospitalisation | 43         | not reported                                             | not reported                                             | not reported                                                      | not reported                                                      |
| DeVore et al33§ | All-cause death or all-cause hospitalisation | 35         | not reported                                             | not reported                                             | not reported                                                      | not reported                                                      |

*Donal et al did not find a significant link between GLS and CV outcomes at 28 months in a continuous Cox proportional hazards regression analysis in 356 patients (univariate analysis: p =0.1406; multivariate analysis: p =0.1192; the HR of this analysis was not reported).19 However, in a post hoc analysis of these data in 348 patients,20 an abnormal GLS (<16% in absolute values) was significantly linked to the combined end point of total mortality or HF hospitalisation at 18 months (HR 1.94 (1.22–3.07)), but an abnormal GLS was not linked to mortality-only at 18 months (HR 1.56 (0.84–2.89)).

†Stampehl et al found in a dichotomous univariate Cox proportional hazards regression analysis that an abnormal GLS (<15% in absolute values) was linked to worse CV outcomes (X²=4.0, p=0.04; the HR of this analysis was not reported). In addition, patients with events had significantly lower GLS than those without events (−11.6 ± 0.4% vs −16.5 ± 0.5%, p=0.03).14

‡Wang et al did not find a significant link in a continuous logistic regression analysis between GLS at rest and CV outcomes (the HR of this analysis was not reported). In line, patients with events had similar values of GLS at rest than those without events (−17.5 ± 3.7% vs −18.8 ± 2.9%, p > 0.05). However, GLS during exercise was significantly linked to CV outcomes (univariate analysis: HR 0.81 (0.72–0.92), p < 0.01; multivariate analysis: HR 0.79 (0.67–0.91), p < 0.01) in a continuous logistic regression analysis. In addition, patients with events had significantly lower GLS during exercise than those without events (−18.2 ± 3.9% vs −21.4 ± 3.9%; p=0.001).30

§DeVore et al did not find a significant link between the tertiles of GLS and a composite end point of time to death or all-cause hospitalisation (p=0.952).33

CV, cardiovascular; GLS, global longitudinal systolic strain (ie, average longitudinal peak systolic strain from ≥12 LV segments); HF, heart failure; HFpEF, heart failure with preserved ejection fraction; MI, myocardial infarction.
Clinical perspectives on the basis of the findings of this meta-analysis

Isolated LV diastolic dysfunction (ie, abnormalities of LV myocardial stiffness and relaxation with normal LVEF) has long been considered the main underlying mechanism in HFrEF.1–3 On the basis of this pathophysiological model, several clinical trials have been conducted to restore the diastolic function of the LV in patients with HFrEF in order to improve the prognosis of these patients.35 36 However, none of these treatments has been shown to decrease mortality in patients with HFrEF.35 36 For this reason, additional pathophysiological mechanisms should be taken into consideration in the design of new clinical trials in this heterogeneous disease. The present meta-analysis analysing 2284 patients with HFrEF and 2302 controls confirms that the longitudinal systolic function of the LV is significantly altered in high proportion of patients with HFrEF. In addition, two large multicentre studies showed that an abnormal LV longitudinal systolic function is significantly linked to CV mortality and HF hospitalisation in these patients. Therefore, we consider that further large multicentre studies with the aim to validate the prognostic relevance of an abnormal GLS in patients with HFrEF are warranted, because if the prognostic role of this LV systolic alteration is confirmed, a future therapeutic target could arise on this complex disease, for which, so far, no effective therapies exist.

LIMITATIONS

Some considerations should be taken into account on this meta-analysis. Given that GLS values could vary among different software packages,37 38 we consider that the cut-off of GLS used to define LV longitudinal systolic dysfunction should be considered according to the ultrasound software package used in each study. In addition, it is worth to note that GLS, like other 2D methods such as LVEF, depends on the imaging quality and for these reasons the patients included in all studies of this meta-analysis had adequate imaging quality for an analysis by 2DSTE. Hence, the results of this meta-analysis could not be extrapolated to patients with poor imaging quality of the LV. Furthermore, while in the present meta-analysis were analysed all published studies that analysed GLS in HFrEF, there was some statistical heterogeneity in GLS values in the study population. In this respect, we performed a meta-regression analysis in order to detect the possible sources of statistical heterogeneity on GLS values among the studies. In effect, we found that the severity of LV filling pressures was the main factor linked to heterogeneity on GLS values among HFrEF studies, whereas the sample size, age and the presence of AF were not linked to GLS values. Nonetheless, it is important to note that it was not possible to perform a subgroup analysis including studies with HFrEF without history of CAD because only one study excluded patients with history of CAD.31

CONCLUSIONS

The present meta-analysis analysing 2284 patients with HFrEF and 2302 controls confirms that the longitudinal systolic function of the LV is significantly altered in high proportion of patients with HFrEF. In addition, two large multicentre studies showed that an abnormal LV longitudinal systolic function is significantly linked to CV mortality and HF hospitalisation in these patients. Therefore, we consider that further large multicentre studies with the aim to validate the prognostic relevance of an abnormal GLS in patients with HFrEF are warranted, because if the prognostic role of this LV systolic alteration is confirmed, a future therapeutic target could arise on this complex disease, for which, so far, no effective therapies exist.

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REFERENCES

1. Zile MR, Baicu CF, Gaasch WH. Diastolic heart failure-abnormalities in active relaxation and passive stiffness of the left ventricle. N Engl J Med 2004;350:1953–9.
2. Brucks S, Little WC, Chao T, et al. Contribution of left ventricular diastolic dysfunction to heart failure regardless of ejection fraction. Am J Cardiol 2005;95:603–6.
3. Westermann D, Kassner M, Steenblik J, et al. Role of left ventricular stiffness in heart failure with normal ejection fraction. Circulation 2008;117:2051–60.
4. Wang J, Khoury DS, Yue Y, et al. Preserved left ventricular twist and circumferential deformation, but depressed longitudinal and radial deformation in patients with diastolic heart failure. Eur Heart J 2008;29:1283–9.
5. Liu YY, Tsai WC, Su CT, et al. Evidence of left ventricular systolic dysfunction detected by automated function imaging in patients with heart failure and preserved left ventricular ejection fraction. J Card Fail 2009;15:782–9.
6. Tan YT, Wenzelburger F, Lee E, et al. The pathophysiology of heart failure with normal ejection fraction: exercise echocardiography reveals complex abnormalities of both systolic and diastolic ventricular function involving torsion, untwist, and longitudinal motion. J Am Coll Cardiol 2009;54:34–46.

7. Morris DA, Gailani M, Vaz Pérez A, et al. Left atrial systolic and diastolic dysfunction in heart failure with normal left ventricular ejection fraction. J Am Soc Echocardiogr 2011;24:651–62.

8. Yip GW, Zhang Q, Xie J, et al. Resting global and regional left ventricular contractility in patients with heart failure and normal ejection fraction: insights from speckle-tracking echocardiography. Heart 2011;97:287–94.

9. Abe H, Caraciolo G, Kheradvar A, et al. Contrast echocardiography for assessing left ventricular vortex strength in heart failure: a prospective cohort study. Eur Heart J Cardiovasc Imaging 2013;14:1049–60.

10. Obokata M, Negishi K, Kurosawa K, et al. Incremental diagnostic value of LA strain with leg lifts in heart failure with preserved ejection fraction. JACC Cardiovascular Imaging 2013;6:749–58.

11. Kraigher-Krainer E, Shah AM, Gupta DK, et al. Impaired systolic function by strain imaging in heart failure with preserved ejection fraction. J Am Coll Cardiol 2014;63:447–56.

12. Menet A, Greffe L, Ennaze PV, et al. Is mechanical dysynchrony a therapeutic target in heart failure with preserved ejection fraction? Am Heart J 2014;168:909–16.

13. Luo XX, Fang F, Lee AP, et al. What can three-dimensional speckle-tracking echocardiography contribute to evaluate global left ventricular systolic performance in patients with heart failure? Int J Cardiol 2014;172:132–7.

14. Stapelh MR, Mann DL, Nguyen JS, et al. Speckle strain echocardiography predicts outcome in patients with heart failure with both depressed and preserved left ventricular ejection fraction. Echocardiography 2015;32:71–8.

15. Shah AM, Claagett B, Swetlitz SI, et al. Prognostic Importance of Impaired Systolic Function in Heart Failure With Preserved Ejection Fraction and the Impact of Spironolactone. Circulation 2015;132:402–14.

16. Kosmala W, Rojek A, Przewlocka-Kosmala M, et al. Contributions of non-diastolic factors to exercise intolerance in heart failure with preserved ejection fraction. J Am Coll Cardiol 2016;67:659–70.

17. Morris DA, Krisper M, Nakatani S, et al. Normal range and usefulness of right ventricular systolic strain to detect subtle right ventricular systolic abnormalities in patients with heart failure: a multicentre study. Eur Heart J Cardiovasc Imaging 2017;18:212–23.

18. Toufan M, Mohammadzadeh Gharebaghi S, Pourafkar L, et al. Systolic longitudinal function of the left ventricle assessed by speckle tracking in heart failure patients with preserved ejection fraction. J Tehran Heart Cent 2015;10:194–200.

19. Donal E, Lund LH, Oger E, et al. New echocardiographic predictors of clinical outcome in patients presenting with heart failure and a preserved left ventricular ejection fraction: a subanalysis of the Ka (Karolinska) Ren (Rennes) Study. Eur J Heart Fail 2015;17:680–8.

20. Donal E, Lund LH, Oger E, et al. Importance of combined left atrial size and estimated pulmonary pressure for clinical outcome in patients presenting with heart failure with preserved ejection fraction. Eur Heart J Cardiovasc Imaging 2017;18:629–35.

21. Carluccio E, Biagioni P, Zuchi C, et al. Fibrosis assessment by integrated backscatter and its relationship with longitudinal deformation and diastolic function in heart failure with preserved ejection fraction. Int J Cardiovasc Imaging 2016;32:1071–80.

22. Iwano H, Kamimura D, Fox ER, et al. Presence and implication of temporal nonuniformity of early diastolic left ventricular wall expansion in patients with heart failure. J Card Fail 2016;22:945–53.

23. Hung CL, Yun CH, Lai YH, et al. An observational study of the association among interstitial adiposity by computed tomography measure, estimated pulmonary pressure, and heart failure outcome in heart failure. Medicine 2016;95:e9312.

24. Huang W, Chai SC, Lee SGS, et al. Prognostic Factors After Index Hospitalization for Heart Failure With Preserved Ejection Fraction. Am J Cardiol 2017;119:2017–20.

25. Ci L, Lai YH, Zhang SN, et al. The associations among co-morbidity, cardiac geometries and mechanics in hospitalized heart failure with or without preserved ejection fraction. Clin Exp Hypertens 2017;1:1–8.

26. Bosch L, Lam CSP, Gong L, et al. Right ventricular dysfunction in left-sided heart failure with preserved versus reduced ejection fraction. Eur J Heart Fail 2017.

27. Phan TT, Shivu GN, Abozguia K, et al. Left ventricular torsion and strain patterns in heart failure with normal ejection fraction are similar to age-related changes. Eur J Echocardiogr 2009;10:793–800.

28. Kasner M, Gaub R, Sinner D, et al. Global strain rate imaging for the estimation of diastolic function in HFNEF compared with pressure-volume loop analysis. Eur J Echocardiogr 2010;11:743–51.

29. Pellicori P, Kallivokacka-Bennett A, Khleva G, et al. Global longitudinal strain in patients with suspected heart failure and a normal ejection fraction: does it improve diagnosis and risk stratification? Int J Cardiovasc Imaging 2014;30:69–79.

30. Wang J, Fang F, Wai-Kwok Yip G, et al. Left ventricular long-axis performance during exercise, is an important prognostic marker in patients with heart failure and preserved ejection fraction. Int J Cardiol 2015;178:131–5.

31. Freed BH, Darwalla V, Cheng JY, et al. Prognostic utility and clinical significance of cardiac Mechanics in heart failure with preserved ejection fraction: importance of left atrial strain. Circ Cardiovasc Imaging 2016;9:e003754.

32. Obokata M, Takeuchi M, Negishi K, et al. Relation Between Echocardiogram-Based Cardiac Parameters and Outcome in Heart Failure With Preserved and Reduced Ejection Fraction. Am J Cardiol 2016;118:1356–62.

33. DeVore AD, McNulty S, Alenez F, et al. Impaired left ventricular global longitudinal strain in patients with heart failure with preserved ejection fraction: insights from the RELAX trial. Eur J Heart Fail 2017;19:893–900.

34. Stewart LA, Clarke M, Rovers M, et al. Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data: the PRISMA-IPD Statement. JAMA 2015;313:1657–65.

35. Zhang Q, Shen Y, Liu Q, et al. Effects of renin-angiotensin-aldosterone system inhibitors on mortality, hospitalization, and diastolic function in patients with HFpEF. A meta-analysis of 13 randomized controlled trials. Herz 2016;41:76–86.

36. Bavishi C, Chatterjee S, Ather S, et al. Beta-blockers in heart failure with preserved ejection fraction: a meta-analysis. Heart Fail Rev 2016;20:193–201.

37. Takigiku K, Takeuchi M, Izumi C, et al. Normal range of left ventricular 2-dimensional strain: Japanese Ultrasound Speckle Tracking of the Left Ventricle (JUSTICE) study. Circ J 2012;76:2623–32.

38. Biaggì P, Carasso S, Garceau P, et al. Comparison of two different speckle tracking software systems: does the method matter? Echocardiography 2012;28:539–47.