Echocardiographic predictors of ventricular arrhythmias in patients with non-ischemic cardiomyopathy

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ABSTRACT

Objective: Ventricular arrhythmias (VA) portend a poor prognosis in non-ischemic cardiomyopathy (NICM). In this meta-analysis we evaluated if left ventricular (LV) global longitudinal strain (GLS) and LV mechanical dispersion (LVMD) are associated with VA, specifically in NICM patients.

Methods: A systematic review and meta-analysis was performed to determine the predictive value of LV GLS and LVMD for VA in NICM patients. VA endpoints were a composite of sudden cardiac death, VA events (including ventricular tachycardia or ventricular fibrillation), cardiac arrest and appropriate implantable cardioverter-defibrillator (ICD) therapy. Hazard or odds ratios for univariate models were extracted for the relationship between LV GLS and LVMD with VA endpoints.

Results: A total of 984 patients from 6 published studies were included; 231 patients (23.5%) experienced the composite endpoint. NICM patients who experienced VA endpoints had LV GLS impairment compared to those without (weighted mean difference =−1.93%; 95% confidence interval (CI) =−2.77 to −1.10; p < 0.001) and LV GLS was related to VA endpoints (hazard ratio: 1.12, 95% CI 1.07−1.17, p < 0.001; odds ratio: 1.22, 95% CI 1.08−1.38, p = 0.002). Four studies reported mean LVMD (weighted mean =−10.05 ms; 95% CI =−22.25 to 8.14; p = 0.28), with 3 reporting risk ratios (1 reported odds ratio and 2 hazard ratios). Only odds ratio demonstrated statistical significance (hazard ratio: 0.47, 95% CI 0.01−22.25, p = 0.70; odds ratio: 1.59, 95% CI 1.14−2.22, p = 0.007).

Conclusion: LV GLS impairment demonstrates value for predicting VA endpoints in NICM patients. Inclusion of LV GLS may be appropriate in the surveillance, screening, and clinical management of NICM patients.

1. Introduction

Myocardial disease with associated ventricular dysfunction in the absence of significant coronary artery disease is broadly referred to as non-ischemic cardiomyopathy (NICM) [1]. NICM encompasses a group of heterogeneous conditions which can be further categorised as dilated, genetic, inflammatory and infiltrative cardiomyopathies [2]. NICM can manifest with LV contractile dysfunction with either a dilated or hypertrophied phenotype [3]. Over time with further tissue injury and development of replacement myocardial fibrosis, a substrate for ventricular arrhythmias (VA) develops, which is a major cause for sudden cardiac death [4]. Death mainly results from heart failure or VA with 3-year mortality rates estimated at 12−20% [4–6]. Studies have demonstrated that implantable cardioverter-defibrillators can reduce mortality in some patients with NICM [5,6]. The current guidelines recommend implantable cardioverter-defibrillator use for primary prevention for left ventricular (LV) ejection fraction ≤35%, New York Heart Association class II–III heart failure and >1 year non-sudden cardiac death expected survival [7]. However, in the real-world setting these criteria are neither sensitive or specific enough to identify NICM patients who are at risk of VA [8,9]. LV global longitudinal strain (GLS) has been demonstrated to be more sensitive for LV dysfunction than LV ejection fraction [10]. Studies have demonstrated LV GLS and additionally LV mechanical dispersion (LVMD) can predict VA in patients with heart failure [11–13]. A recent meta-analysis that combined both ischemic and non-ischemic cardiomyopathy groups, demonstrated that...
LVMD in particular has an important predictive value for VA [14]. However, the majority of the cohort in this report were ischemic cardiomyopathy (ICM) patients, which has a different pathophysiology and myocardial fibrosis location as compared to NICM patients [14]. No information exists in this regard specific to NICM patients; as such studies focused exclusively on NICM patients have relatively small sample size and are often limited to a single centre [13,15]. The aim of this study was to evaluate the association between LV GLS and LVMD with VA endpoints, specifically in NICM patients by undertaking a meta-analysis to allow deeper insights and strengthen the level of evidence.

2. Methods

A search was conducted on 5 electronic databases which included Cochrane, Embase, PubMed, Scopus and Web of Science. The search was conducted using the terms ‘mechanical dispersion’, ‘2D strain’, ‘2-dimensional strain’, ‘speckle tracking’, ‘strain’, ‘dispersion’, ‘non-ischemic cardiomyopathy’, ‘non-ischemic heart disease’, ‘arrhythmogenic right ventricular cardiomyopathy’, ‘NICM’, ‘dilated cardiomyopathy’, ‘idiopathic cardiomyopathy’, ‘cardiomyopathy’, ‘sudden death’, ‘VT’, ‘ventricular tachycardia’, ‘ventricular fibrillation’, ‘ventricular arrhythmia’ and ‘implantable cardioverter defibrillation’. This search incorporated all studies from the database commencement till 22nd September 2020. Articles identified as systematic reviews or meta-analysis papers had the reference lists reviewed to identify further possible articles. The search strategy, inclusion and exclusion process are demonstrated in Fig. 1.

Studies that evaluated the prediction of VA endpoints in non-ischemic cardiomyopathy patients using 2-dimensional speckle tracking of the LV on transthoracic echocardiography were identified and included in this analysis. All studies which had the requisite information on echocardiographic LV strain (measured as global longitudinal strain) and longitudinal follow up for death and ventricular arrhythmias in NICM patients were included. LV GLS in the identified studies was defined as derived from 2D speckle tracking analysis from the 3 apical 2-, 4- and long-axis views (Fig. 2A) [16]. These articles were further reviewed and incorporated for analysis if data was provided regarding the ability of LV GLS to predict ventricular arrhythmias in non-ischemic cardiomyopathy patients. Studies which were duplicates, conference abstracts, book sections, case reports, congress reports, editorials, guidelines, review articles, meta-analysis, conference posters and clinical trials were excluded from this analysis. Identified guidelines, review articles and meta-analysis were further scrutinised through review of selected article reference lists to identify any further studies which could be incorporated in this analysis. Studies which incorporate animal studies or paediatric patients were also excluded from this analysis. Further exclusion criteria are shown in Fig. 1.

Within the identified studies further analysis was performed using LVMD as a predictor of VA endpoints in NICM patients if the data was available. LVMD was calculated as the standard deviation of the time from Q/R wave on electrocardiography to peak negative strain within each LV segment (Fig. 2B) [17].

The primary composite VA endpoints included sudden cardiac death, VA events (including documented ventricular tachycardia or ventricular fibrillation), cardiac arrest and appropriate implantable cardioverter-defibrillator (ICD) therapy.

Data extraction was performed by 2 investigators (MH and MZ) independently. Manual review was performed for any discrepancies found which were resolved by consensus. The following data was extracted from the included studies: study design, number of patients, mean age, gender numbers, non-ischemic cardiomyopathy type, follow-up periods, transthoracic echocardiogram (TTE) vendor and software, echocardiographic parameters (including LV ejection fraction [LVEF], LV global longitudinal strain [GLS] and LV mechanical dispersion [LVMD]). Hazard and odds ratios were pooled together for analysis from included studies where displayed.

Continuous variables were reported as weighted means after data extraction was performed for the continuous variables of the studies. The weighted mean difference was calculated for both LV GLS and LVMD in the included studies for patients with and without VA endpoints. A random effects model that was adjusted for clinical differences between the populations was used to calculate pooled hazard ratios (HR)
and odds ratios (OR) with 95% confidence interval (CI) to determine the association of VA endpoints to LV GLS and LVMD, further demonstrated utilising Forest plots. LVMD HR were either displayed relative to 1 ms increase or 10 ms increase and to ensure consistency we rescaled all LVMD HR to 10 ms increases. Study heterogeneity was expressed using the $I^2$ statistic. In this study a p-value $< 0.05$ was considered to be statistically significant. All statistical analysis was performed using Review Manager (RevMan) Version 5.4 (The Cochrane Collection, London, United Kingdom).

3. Results

The initial search returned a total of 2133 articles. Once the articles were reviewed with the specific inclusion and exclusion criteria, 6 articles remained for further analysis (Fig. 1) [18–23]. Details of the included studies are demonstrated in Table 1. All included studies were observational, with 5 being prospective and 1 being a retrospective study. There was a total of 984 patients with a weighted mean age of 53 (40% female). The included studies all used General Electric (GE) ultrasound systems, and most have used the GE Echopac software for offline analysis of LV GLS and LVMD, with the exception of 1 study that used the Ultra Extend, Toshiba Medical Systems (Table 1) for obtaining strain measurements.

Baseline echocardiographic details from all included studies are displayed in Table 1. Five studies reported mean LVEF and LV GLS, but only 4 studies reported mean LVMD, with 1 reporting median values for LVEF, LV GLS and LVMD. The weighted mean LV GLS was $-13.9\%$ (LV GLS ranged from $-9.1$ to $-17\%$) and weighted mean LVMD was $79.7$ ms (LVMD ranged from 60 to 103 ms). Intraclass coefficient for both intra-observer and inter-observer GLS variability was reported in 4 studies which ranged from 0.91 to 0.99 and 0.92 to 0.99, respectively (Table 2). LVMD intra-observer and inter-observer variability was recorded in 4 studies and ranged from 0.91 to 0.99 and 0.88 to 0.94, respectively (Table 2).

There were 231 patients who experienced VA endpoints in the studies which reported mean LV GLS. This demonstrated that LV GLS was more impaired in NICM patients who experienced VA endpoints as opposed to those patients who did not (Fig. 3). LV GLS was 1.93\% (p $< 0.01$) more impaired in NICM patients who experienced VA endpoints compared to those who did not (Fig. 3).

There were 3 studies which reported LVMD risk ratios and included 107 patients who experienced VA endpoints. Analysis demonstrated that LVMD was 10.05 ms shorter in those patients who did not experience VA endpoints but did not reach statistical significance (p $< 0.28$) (Fig. 4).

The included studies reported risk variables for LV GLS as either OR or HR; 2 studies reported OR and 4 studies reported HR. Association of LV GLS using univariate models for OR and HR is displayed in Fig. 5A and B, respectively. LV GLS displayed a significant association with VA endpoints in NICM patients. The pooled OR of LV GLS from 2 studies for VA endpoints was 1.22 (95% CI: 1.08–1.38; p $= 0.002$; $I^2 = 0\%$). The
Table 1
Study design, patient demographics, ventricular arrhythmia event details and echocardiographic parameters from included studies.

Table 1A

| First Author (reference number) | Year | n  | Study Design | Age (years) | Male (%) | Population | Endpoints | Follow-up Period (years) |
|---------------------------------|------|----|--------------|-------------|----------|------------|-----------|-------------------------|
| Debonnaire et al. [18]           | 2014 | 92 | Prospective  | 50 ± 14     | 68.5     | Hypertrophic cardiomyopathy | Appropriate ICD therapy | 4.7 (Range: 2.2–8.2)     |
| Haland et al. [19]†              | 2016 | 200 (50 were control) | 54 ± 14 | 60.7 | Hypertrophic cardiomyopathy and control patients | Cardiac arrest and Ventricular tachycardia | No follow-up period specified |
| Hiemstra et al. [20]             | 2016 | 427 | Prospective  | 52 ± 15     | 66       | Hypertrophic cardiomyopathy | Appropriate ICD therapy | 6.7 (Range: 3.3–10)      |
| Matsuzoe et al. [21]             | 2016 | 72  | Retrospective | 58 ± 15     | 81.9     | Undifferentiated non-ischemic cardiomyopathy | Appropriate ICD therapy | 1.4 (Range: 0.02–6.04)   |
| Negishi et al. [22]              | 2016 | 124 | Prospective  | 56 ± 13     | 54       | Idiopathic, chemically-related, viral, alcoholic and peripartum cardiomyopathy | Appropriate ICD therapy | 3.8 (Interquartile range: 2.2–6) |
| Sarvari et al. [23]†             | 2011 | 69  | Prospective  | 43.7 ± 15.9 | 37.7 | Arrhythmogenic right ventricular cardiomyopathy | Ventricular tachycardia and ventricular fibrillation | No follow-up period specified |

Table 1B

| First Author (reference number) | VA Endpoints | Vendor | Software | LVEF (%) | LV GLS (%) | LVMD (ms) |
|---------------------------------|--------------|--------|----------|----------|------------|-----------|
| Debonnaire et al. [18]          | 21           | GE     | Echopac  | 70 (64–76) | −13.3 ± 3.5 | NR        |
| Haland et al. [19]†             | 37           | GE     | Echopac  | 61 ± 8   | −15.7 ± 3.6 | 64 ± 22   |
| Hiemstra et al. [20]            | 63           | GE     | Ultra Extend | 65 ± 9 | −15 ± 4 | NR        |
| Matsuzoe et al. [21]            | 34           | GE     | Echopac  | 52.2 ± 12 | −11 ± 3.4 | 83.1 ± 28.6 |
| Negishi et al. [22]             | 36           | GE     | Echopac  | 31.4 ± 9.9 | −9.1 ± 3.5 | 103 ± 43  |
| Sarvari et al. [23]†            | 42           | GE     | Echopac  | 60 (55–67) | −17 (16–19) | 60 (48–70) |

*Values are expressed either as mean ± standard deviation or median (interquartile range) for Table 1A and 1B.
†Studies which reported odds ratios with no specified follow-up period.
‡Studies which reported risk variables for LVMD: 1 study as HR (Supplemental Fig. 1A and B). The LVMD risk variables were all expressed per 10 ms increases to allow comparison.
§Abbreviations: ICD = implantable cardioverter-defibrillator, VA = Ventricular arrhythmias, LV = Left ventricle, LVEF = LV ejection fraction, GLS = Global longitudinal strain, LVMD = LV mechanical dispersion, GE = General electric, NR = Not reported.

Table 2

| First Author (Reference Number) | Method | LV GLS | Intraobserver Variability | Interobserver Variability |
|---------------------------------|--------|--------|---------------------------|--------------------------|
| Debonnaire et al. [18]          | NR     | NR     | NR                        | NR                       |
| Haland et al. [19]†             | ICC 0.95 | 0.96   |                           |                          |
| Hiemstra et al. [20]            | ICC 0.91 | 0.94   |                           |                          |
| Matsuzoe et al. [21]            | NR     | NR     | NR                        | NR                       |
| Negishi et al. [22]             | ICC 0.99 | 0.99   |                           |                          |
| Sarvari et al. [23]†            | ICC 0.94 | 0.94   |                           |                          |

*Abbreviations: LV = Left ventricle, GLS = Global longitudinal strain, NR = Not reported, ICC = Intraclass correlation coefficient.

pooled HR of LV GLS from 4 studies for VA endpoints was 1.12 (95% CI: 1.07–1.17; p < 0.001; I² = 0%). Additionally, 3 studies reported risk variables for LVMD: 1 study as OR and 2 studies as HR (Supplemental Fig. 1A and B). The LVMD risk variables were all expressed per 10 ms increases to allow comparison. The OR for LVMD association with VA endpoints was 1.59 (95% CI: 1.14–2.22; p = 0.007) in 1 study. The pooled HR for LVMD association with VA endpoints was 0.47 (95% CI: 0.01–22.25; p = 0.7; I² = 32%) but did not reach statistical significance.

All studies had quality assessment performed utilizing the Newcastle-Ottawa Quality Assessment Tool [24]. Each article which was included in this analysis was reviewed against a set of criteria dependent on the article being either a case-control or cohort study. The 6 included studies were evaluated with all studies receiving a score of 8 points or higher on the Newcastle-Ottawa scale. This demonstrated that the included studies were of high quality.

4. Discussion

This study highlights important findings on the utility of non-invasive advance echocardiographic parameters, rather than the current recommendation of LVEF, for risk stratification in NICM patients. However, the number of appropriate studies (ie. limited to NICM patients) that could be included in this metaanalysis was small. Notwithstanding the relatively small number of published studies, the main findings of our study from 984 NICM patients are that NICM patients who experienced VA endpoints had significantly greater impairment in...
LV GLS than those who did not experience VA endpoints, thus suggesting an important role in VA prediction. Furthermore, on pooled analysis of the LV GLS risk variables from prior studies a significant association was demonstrated with VA endpoints. LVMD was also analysed as an echocardiographic predictor of VA endpoints in NICM patients. The results did not reach statistical significance to demonstrate an association; however, this analysis was limited because of the relatively small number of studies reporting LVMD association with VA endpoints in NICM patients.

NICM is a heterogenous group of diseases, unlike patients with ICM who are a more homogenous group [1]. NICM is divided into primary and secondary cardiomyopathies [1]. Further primary cardiomyopathies can be further subdivided into genetic, mixed and nongenetic acquired disorders [1]. It has been demonstrated that the mechanism for VA is re-entrant circuits caused by myocardial fibrosis, irrespective of the specific NICM etiology [25]. The pathophysiology between NICM and ICM are quite different. The distribution of myocardial fibrosis can be vastly different in these groups, with ischemia resulting in endocardial or transmural scar, while in NICM fibrosis is usually isolated to the epicardium or midwall [26–28]. A recent metanalysis in predominantly ICM patients, demonstrated that LVMD was superior to both LVEF and LV GLS, and may reflect specifically the role of contraction heterogeneity in development of VA events in NICM patients [14].

Studies have suggested conflicting views regarding the benefit of ICD therapy in NICM patients compared to ICM in preventing sudden cardiac death [6,29]. One challenge that has likely resulted in such inconsistent findings has been the limited ability to predict the occurrence of VA endpoints in NICM patients utilising LVEF [5,29–32]. Despite the heterogeneity of NICM patients and differing pathological processes involved, our study suggests that LV GLS can provide additional utility in risk stratification of NICM patients for the occurrence of VA endpoints. Given the small number of studies that evaluated LVMD, we are unable to demonstrate definitive results on its utility in predicting VA events in NICM patients.

The risk of sudden cardiac death or arrhythmias is increased in all cardiomyopathy subtypes correlating often with the presence and extent of fibrosis or scar [27,29]. Several studies have demonstrated this in ICM, but this is also increasingly being recognized among NICM patients who experience VA [33–36]. Cardiac magnetic resonance imaging (cMRI) has been an important tool in identifying scar in NICM patients [37], and the evidence of late gadolinium enhancement has been shown to be valuable [38]. A meta-analysis has demonstrated that identification of myocardial fibrosis using late gadolinium enhancement on cMRI can help guide risk stratification for VA endpoints in NICM patients [38]. This study included 1488 patients compiled from 9 studies which was comparable to the number of patients and studies included in this meta-analysis. There were higher number of patients experiencing the composite primary endpoint which was more diverse (including all-cause mortality, heart failure hospitalization, and a composite end point of sudden cardiac death (SCD) or aborted SCD, in comparison to this study [38]. However, cMRI has limitations as it is expensive, not widely available, gadolinium cannot be administered in those with renal dysfunction, image degradation can occur from implantable cardioverter defibrillator lead artefact, and some patients may not tolerate long scanning times. LVGLS has shown correlation with fibrosis/scar identified on cMRI [39,40].
Echocardiography is widely available and is relatively inexpensive and could be utilised in risk stratification in NICM patients. Areas of scar can be visually evaluated as regional wall motion abnormality in severe cases. Current guidelines utilise LVEF as an echocardiographic measure in risk stratification for VA endpoints in NICM patients [7]. However, LVEF remains a ‘blunt’ measure with limited ability in risk stratification, as some NICM patients with preserved LVEF still experience VA endpoints [41]. Despite LVEF having some prognostic value in NICM patients, it was demonstrated that myocardial scar has a strong incremental prognostic value for sudden cardiac death [42]. More recently it was demonstrated that echocardiographic LV GLS has good correlation with myocardial scar with improved prognostic value compared to LVEF [16,43]. Thus, LV GLS could be utilised for patient risk stratification in predicting VA endpoints, as demonstrated in this meta-analysis than LVEF. Future studies could evaluate the additive value of combining cMRI scar with LV GLS in risk stratification of NICM patients.

Our meta-analysis incorporated studies with variations in both the inclusion criteria and endpoints with, possible sources of heterogeneity in the included studies. However, NICM typically includes heterogeneous patient groups. Additionally, individual patient level data was not available to adjust for other co-variables that may influence VA endpoint incidence such as other imaging or biochemical parameters and medication history. There were only a relatively small number of studies that met the inclusion criteria that were finally included in this meta-analysis which may result in an overestimation of the pooled effect sizes. In particular, there was limited evaluation of LVMD, sensitivity analysis and evaluation of publication bias could not be determined due to small number of studies and limited data that was provided. However, what this highlights is the need for future prospective multicentre studies of a larger group of NICM patients are required to further confirm the relationship between LV GLS and LVMD with VA endpoints.

Myocardial strain is a measure which is dependent on several factors including echocardiographic 2-dimensional image quality with appropriate image settings; assessment of LV GLS in centres with less experience may have an unclear impact. However, on review of the available reproducibility measures for intraclass and interclass correlation coefficients, they were similar between studies and variability was low overall for LV GLS (Table 2). Intervendor and software standardization has often been identified as a possible limitation for myocardial strain. All included studies in this meta-analysis used a single vendor system (General Electric, GE) and 5 out of 6 used Echopac software to calculate LV GLS (Table 1B). Moreover, there was a call for standardization by vendors by the echocardiography societies, that has substantively reduced differences in LV GLS obtained from various vendor platforms [44].

5. Conclusions

Our study demonstrates that LV GLS has predictive value for VA endpoints in NICM patients, independent and incremental to LVEF. Therefore, the routine use of LV GLS should be considered to non-invasively assess the risk for VA endpoints in NICM patients. Utilising echocardiographic LV GLS may be of particular relevance when cMRI cannot be easily accessed and may provide additional value for patient risk stratification in such instances. Further prospective studies are required to validate our findings and integrate LV GLS into decision making and guidelines for ICD implantation in NICM patients.

Declaration of Competing Interest

The authors report no relationships that could be construed as a conflict of interest.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jichi.2022.100962.

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