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Normal Ranges of Right Ventricular Systolic and Diastolic Strain Measures in Children: A Systematic Review and Meta-Analysis

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Abstract

Background—Establishment of the range of normal values and associated variations of two-dimensional speckle-tracking echocardiography (2DSTE) derived right ventricular (RV) strain is a prerequisite for its routine clinical application in children. The objectives of this study were to perform a meta-analysis of normal ranges of RV longitudinal strain measurements derived by 2DSTE in children and identify confounders that may contribute to differences in reported measures.

Methods—A systematic review was launched in PubMed, Embase, Scopus, Cochrane, and ClinicTrials.gov. Search hedges were created to cover the concepts of pediatrics, speckle-tracking echocardiography, and right heart ventricle. Two investigators independently identified and included studies if they reported the 2DSTE derived RV strain measures: RV peak global longitudinal strain (pGLS), systolic strain rate (pGLSRs), early diastolic strain rate (pGLSRe), late diastolic strain rate (pGLSRa), or segmental longitudinal strain at the apical, mid, and basal ventricular levels in healthy children. Quality and reporting of the studies were assessed. The weighted mean was estimated by using random-effects with 95% confidence intervals (CI), heterogeneity was assessed by the Cochran's Q statistic and the inconsistency index (I^2), and publication bias was evaluated using funnel plots and the Egger test. Effects of demographic, clinical, equipment, and software variables were assessed in a meta-regression.

Results—The search identified 226 children from 10 studies. The reported normal mean values of pGLS among the studies varied from −20.80% to −34.10% (mean, −29.03%, 95%CI, −31.52% to −26.54%), pGLSRs varied from −1.30 to −2.40 1/sec (mean, −1.88, 95%CI, −2.10 to −1.59), pGLSRe ranged from 1.7 to 2.69 1/sec (mean, 2.34, 95%CI, 2.00 to 2.67) and pGLSRa ranged from 1.00 to 1.30 1/sec (mean, 1.18, 95% CI, 1.04 to 1.33). A significant base-to-apex segmental strain gradient ($p < 0.05$) was observed in the right ventricular free wall. There was significant

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between-study heterogeneity and inconsistency (I^2>88% and p<0.01 for each strain measure), which was not explained by age, gender, body surface area, heart rate, frame rate, tissue tracking methodology, equipment, or software. The meta-regression showed that these effects were not significant determinants of variations among normal ranges of strain values. There was no evidence of publication bias (Egger test, p=0.59).

Conclusions—This study is the first to define normal values of two-dimensional speckle tracking echocardiographic (2DSTE) derived right ventricle strain in children on the basis of a meta-analysis. The normal mean value in children for RV global strain is −29.03% (95% CI, −31.52% to −26.54%). The normal mean value for RV global systolic strain rate is −1.88 1/sec (95% CI, −2.10 to −1.59). RV segmental strain has a stable base-to-apex gradient that highlights the dominance of deep longitudinal layers of the RV that are aligned base to apex. Variations among different normal ranges do not appear to be dependent on differences in demographic, clinical, or equipment parameters in this meta-analysis. All of the eligible studies used equipment and software from one manufacturer, General Electric (GE).

Keywords

Right Ventricle; cardiac function; Global Longitudinal Strain; Speckle Tracking Echocardiography; Children

Introduction

Right ventricular (RV) function is an important prognostic determinant of cardiopulmonary pathologies in children (1–4). The RV myofiber architecture is composed of superficial oblique and dominant deep longitudinal layers, but the longitudinal shortening is the dominant deformation of the RV that provides the major contribution to stroke volume during systole (5). Myocardial strain that describes this longitudinal deformation under an applied force provides a new sensitive measure of the RV function in children (4,6). Two-dimensional speckle tracking echocardiography (2DSTE) is an angle-independent method for myocardial strain measurement that has been used to estimate deformation measures and quantitatively characterize cardiac function in children (7–10).

Utilization of myocardial strain parameters derived by 2DSTE to measure RV function in children requires knowledge of the range of normal values (11). Clinical applications of strain imaging to assess systolic and diastolic function in children with a variety of complex conditions (congenital heart disease, cystic fibrosis, sickle-cell anemia, and chronic lung disease) have recently reported measures of global and segmental longitudinal strain and strain rate. (12–24). However, the mean values and associated variations of these strain values need to be firmly established before routine clinical adoption of RV strain measurements can be implemented in children (11).

There are several potential sources of variation between the reported values in studies that may influence the acquisition and generation of strain measures, specifically patient demographics (age, gender, race) clinical factors (HR, blood pressure, weight or body surface area), as well as equipment and image technique variables (ultrasound and vendor customized software, probe size, tissue tracking methodology, and frame rate). (25). Similar

to Yingchoncharoen et al's. 2012 meta analysis on the normal ranges of left ventricular strain in adults, we sought to define a range of normal RV strain measures by utilizing a compilation of all studies that reported values for normal or control children cohorts (25). The objectives of our study were to perform a meta-analysis of normal ranges of RV longitudinal strain and strain rate measurements derived by 2DSTE in children and identify confounders that may contribute to differences and variability in reported measures.

Methods

Search Strategy/Search Protocol

SF, our librarian trained in systematic reviews, created search hedges to cover the concepts of pediatrics/children, speckle tracking echocardiography, and right heart ventricles using terms harvested from standard term indices and on-topic articles (appendix 1). To exclude animals, SF used the Human filter for PubMed, recommended in Cochrane Handbook for Systematic Reviews of Interventions, and then employed that as a model to create similar filters for the other searched databases (26). The search strategy was launched in PubMed, Embase, Scopus, CENTRAL (Cochrane Central Register of Controlled Trials), and ClinicalTrials.gov. Searches were completed by May 2013.

Study Selection/Eligibility criteria

Studies were included if the articles reported using strain derived by two-dimensional speckle-tracking echocardiography to measure RV function in healthy pediatric normal or control subjects. Studies that exclusively included children < 21 years of age were considered eligible for the meta-analysis. The systematic review incorporated observational studies that used pediatric control groups with normal results on echocardiography (who were recruited for specific studies) or if the children were the primary objective (12–24).

Seven specific global and segmental strain and strain rate measurements were included in the meta-analysis. The global longitudinal strain measures included: (1) peak global longitudinal strain (pGLS) within the systolic period; (2) systolic strain rate (pGLSRs); (3) early diastolic strain rate (pGLSRe); and (4) late diastolic strain rate (pGLSRa). The segmental longitudinal strain measures included segmental longitudinal strain at the (5) apex, (6) mid, and (7) basal ventricular levels of the RV free wall (SLS-Apex, SLS-Mid, SLS-Base, respectively). Studies were excluded from this analysis if they were abstracts only without full text or review articles (25). All echocardiographic strain measurements are generated from digitally stored images. Currently, there are two reported methods to generate RV "global" longitudinal strain measures from the apical four-chamber view (figure 1). Method 1: *Full RV Myocardium*: Global longitudinal myocardial deformation can be calculated based on the entire traced contour of the right ventricles that includes the right ventricular free wall and the septal wall (21); and Method 2: *Right Ventricle Free wall (RVFW)*: The weighted average of the three regional values of the lateral RV free wall only (basal, mid, and apical segments) provide the value of global longitudinal RV strain (23,24,30) (figure 1). We stratified our meta-analysis by the "*Full RV Myocardium*" vs. "*RVFW* only" methods of reporting "global" RV strain and strain rate to account for the different techniques utilized between studies.

Data Collection

Each eligible article meeting the inclusion criteria was reviewed by two independent reviewers (P.T.L and A.S), and the following data was extracted and entered into an electronic database: (1) *Study*: first and last authors, year of publication; (2) *demographic*: number of controls subjects, age, gender; (3) *clinical*: (heart rate (HR), body surface area (BSA); and (4) *echocardiographic parameters*: (vendor customized ultrasound, vendor customized software, probe frequency, frame rate, tissue tracking methodology, and number of cardiac cycles acquired). All the authors of the eligible studies (12–24) were contacted by electronic mail to notify them of the meta-analysis and obtain any missing information not reported in their individual studies.

Quality Assessment

To assess the quality and reporting of studies, we evaluated 12 items that were considered relevant to this systematic review and meta analysis topic, based on the quality assessment methodology of Downs et al. 1998 (Appendix 2) (27). Two reviewers (P.T.L. and A.S.) independently assessed the quality items, and discrepancies were resolved by consensus. These items covered the quality of reporting, external validity and, internal validation for each study. For strain imaging, the authors postulated that the most important quality assessment parameters are related to (1) study documentation of intra- and inter- observer reproducibility of strain measurements, (2) documentation of patient blood pressure and heart rate, (3) the blinding to patient outcomes of the individuals acquiring the images and the observers generating the measures, and a (4) protocol for image acquisition and data analysis.

Statistical Analysis/Data Synthesis

Meta-analysis was performed using STATA version IC 12 (StataCorp LP, College Station, TX). The means and 95% confidence intervals (CI) of strain measures were computed using random-effects models weighted by inverse variance. Between-study statistical heterogeneity was assessed using the Cochran Q statistic and was quantified using the I^2 method by measuring inconsistency (I^2, the percentage of total variance across studies attributable to heterogeneity rather than chance). These results were presented as a forest plot, which is the standard way to illustrate results of individual studies and meta-analyses. (26–30) The forest plot was used as a graphical display of the relative strength of the effect estimates and confidence intervals for each of the individual studies and the entire meta-analysis. (26–30) The forest plot is presented with five columns: (1) The left hand column lists the names of the included studies in chronological order; (2) the second column is the plot of the measure of effect for each of these studies. Each study is represented by a square that reflects the mean at the point estimate of effect and is proportional to the study's weight in the meta-analysis (quantitatively described in column four). A horizontal line extending from either side of the square reflects the 95% confidence interval. The overall meta-analysis measure of effect is plotted as a diamond with the lateral points of the diamond indicating confidence intervals for this mean estimate. The dashed vertical line through the middle of the diamond is the mean estimate of the meta-analysis and provides a reference line for each individual study; (3) the third column is the mean value for each study with

upper (95%) and lower (5%) limits; (4) the fourth column is the study weights; and (5) the fifth column lists the number of subjects in each study (26–30).

Publication bias was assessed using funnel plots and the Egger test. A funnel plot is a scatter plot of the effect estimates from individual studies against a measure of each study's size. (26,27) It is a qualitative visual assessment utilized to check the existence of publication bias in meta-analyses. The standard error of the effect estimate is chosen as the measure of study size and plotted on the vertical axis. The mean of the strain measures is plotted on the horizontal axis. The larger studies will be near the average of the meta-analysis, the centerline, and small studies will be on both sides of the average. A symmetrical distribution of studies in the funnel plot would suggest the absence of publication bias. (26,27) However, visual interpretation of funnel plot may be too subjective because statistical power is determined by factors in addition to sample size. (26) The funnel plot was therefore combined with the Egger test, a linear regression statistical analysis of the effect estimated against its standard error, and used for continuous outcomes with effects measured as mean differences. (26) Finally, there are a number of important variables that may influence the differences in the reported strain measures among studies (25), and the source of these variations was sought between studies using meta-regression to estimate the percent of heterogeneity on the influence of the variation in normal strain measurements (28–30).

Results

Eligibility Criteria

An initial search identified 268 articles. After excluding duplicates and triplicates (90), there were 178 studies screened for relevance. Articles not exclusively in children (60), articles unrelated to the topics (53), abstracts without text or reviews (39), and articles that did not have data on controls or normal children (13) were then excluded. Searching the bibliographies did not reveal any additional results. No ongoing studies were found in the clinical trials registries. Thirteen published observational or case control studies met inclusion criteria (Figure 2). Three sets of articles used overlapping control population datasets (14 and 15, 19 and 20, 23 and 24). The first or last authors of each of these studies were contacted by electronic mail, and one control dataset was either provided or chosen based on author recommendation (Table 1 and Table 2). In total, 10 datasets of strain measures from 13 studies of strain measures with 226 children were considered eligible for assessment in the meta-analysis (figure 2). All the studies that met search criteria were in English, although the search criteria were not only limited to English manuscripts.

Study Selection Based on Strain Measures

All 10 datasets (13 articles) with 226 patients were eligible for the meta-analysis of pGLS (12–24). From the 10 datasets, 6 datasets with 136 patients reported pGLSRs and were included in the meta-analysis of pGLSRs (13–15,17–20,22), 5 datasets with 116 patients were eligible for the meta-analysis of pGLSRe (14–15,17–20,22), and 4 datasets with 67 patients were eligible for the meta-analysis of pGLSRa (17–20,22). In addition, from the 10 datasets, 5 datasets with 100 patients reported segmental strain measures at the apex, mid and basal ventricular levels of the RVFW, and were analyzed in the meta-analysis of

segmental strain (13,16,18–20,23,24). The patient characteristics of the included studies are listed in Table 1. The echocardiographic variables included from the studies are listed in Table 2.

Study Quality Assessment

Critical appraisal of the studies could not demonstrate high quality in all the studies included (Appendix 2 and Appendix 3). All studies clearly defined the objectives, the primary outcomes that were measured, and the main findings. The majority also reported patient characteristics and described the confounding factors that might affect the acquisition and processing of strain measurements in children, however, they did not all document the blood pressure. All the studies utilized a detailed strain image acquisition and data processing protocol. None of the studies clearly stated how many echo-sonographers acquired the images and their training level with regard to 2DSTE image acquisition. There were only a few studies that specified how many individuals performed the data analysis and if they were blinded to the patient outcomes (12,18–20). Intra- and inter- observer reproducibility analysis was performed in 6/10 datasets, (12–15,18–21) and referenced in 3/10 (17,22–24).

Normal Ranges

Global Longitudinal Strain Measures

Global Strain (%): We stratified the meta-analysis by the "*Full RV Myocardium*" vs. "*RVFW* only " methods of reporting "global" RV strain and strain rate to account for the different techniques utilized between studies. Of the 10 eligible datasets in this meta-analysis, five datasets used the *Full RV Myocardium* method (16–21) and five datasets employed the *RVFW* only method (12–15,22–24) when reporting normal values for "global" longitudinal RV Strain. Normal mean values of pGLS for all the ten datasets combined varied from −20.80% to −34.10% (mean −29.03, 95% CI −31.52 to −26.54) (Figure 3a). Between-study heterogeneity was evidenced by a Cochran's Q statistic of 165.98 ($P < 0.0001$) and inconsistency by an I^2 value of 94.6%. The heterogeneity was not explained by the different techniques (*Full RV Myocardium* vs. *RVFW* only) to acquire global strain. In addition, the heterogeneity was not explained by age, gender, BSA, heart rate, tissue tracking methodology, frame rate, or probe size. Normal mean values of pGLS for the *RVFW* only method ranged from −20.80% to −34.10, (mean −30.06, 95% CI −32.91 to −27.21). Normal mean values for pGLS for the *Full RV Myocardium* method ranged from −23.56% to −31.90% (mean −28.20, 95%CI −31.52 to −24.88).

Age and Global Strain (%): Age did not explain the heterogeneity of the reported normal ranges of values for peak global longitudinal strain. The breakdown of the age distribution for the studies was: four data-sets recruited patients 0–9 years of age (12,17–20), four datasets had patients with age ranges of 10–13 years of age (13–16), and 2 datasets examined patients with age ranges 14–21 years of age (22–24). We performed a separate meta-analysis stratified by age distribution using the mean age from each study as a continuous variable and also by categorizing each study into one of the three age distribution categories, 0–9, 10–13, and 14–21. The Cochran Q statistic ranged from 17.59 to 82.13 (P <

0.0001) and the I^2 value remained the same in both methods and ranged from 93.9%–95.1% (Figure 3b).

Global Systolic Strain Rate (1/sec): Six out of the ten eligible datasets reported global longitudinal systolic strain rate (pGLSRs) (13–15,17–20,22). Of theses six datasets, 3 used the *Full RV Myocardium* method (17–20), and 3 employed the *RVFW* only method (13–15,22). Normal mean values of pGLSRs for all the six datasets combined varied from −1.30 to −2.40 (Mean, −1.88; 95% CI, −2.18% to −1.59). Between-study heterogeneity was evidenced by a Cochran's Q statistic of 59.2 ($P < 0.0001$) and inconsistency by an I^2 value of 91.7%. The heterogeneity was not explained by different techniques (*Full RV Myocardium* vs. *RVFW* only) to acquire pGLSRs. In addition, the heterogeneity was not explained by age, gender, BSA, heart rate, tissue tracking methodology, frame rate, or probe size. Normal mean values of pGLSRs for the *RVFW* method ranged from −1.58 to −2.01, (mean –1.79, 95% CI −2.08 to −1.50). Normal mean values for pGLSRs for the *Full RV Myocardium* method ranged from 2212;1.30 to −2.40 (Mean, −1.97; 95% CI, −2.48% to −1.45) (Figure 4).

Global Early Diastolic Strain Rate (1/sec): Five out of the ten eligible datasets reported global longitudinal early diastolic strain rate (pGLSRe) (14–15,17–20,22). Of theses five, 3 datasets used the *Full RV Myocardium* (17–20) method, and 2 studies employed the *RVFW* method (14,15,22). Normal mean values of pGLSRe for all the five datasets combined varied from 1.70 to 2.69 (Mean 2.34, 95% CI, 2.00 to 2.67). Between-study heterogeneity was evidenced by a Cochran's Q statistic of 29.4 ($P < 0.0001$) and inconsistency by an I2 value of 86.4%. The heterogeneity was not explained by different techniques (*Full RV Myocardium* vs. *RVFW* only) to acquire pGLSRe. In addition, the heterogeneity was not explained by age, gender, BSA, heart rate, tissue tracking methodology, frame rate, or probe size. Normal values of pGLSRs for the *RVFW* method ranged from 2.12 to 2.60, (mean 2.40, 95% CI 2.06 to 2.74). Normal values for pGLSRs for the *Full RV Myocardium* method ranged from 1.70 to −2.69 (Mean, 2.20; 95% CI, 1.23% to 3.17)

Global Late Diastolic Strain Rate (1/sec): Four out of the ten eligible datasets reported global longitudinal late diastolic strain rate (pGLSRa) (17–20,22). Of theses four, 3 datasets used the *Full RV Myocardium* method (17–20), and one dataset employed the *RVFW* only method (22). Normal mean values of pGLSRa for all the four datasets combined varied from 1.00 to 1.30 (Mean 1.18, 95% CI, 1.04 to 1.33). Between-study heterogeneity was not evidenced by a Cochran's Q statistic of 4.13 ($P=0.248$) and inconsistency by an I^2 value of 27.3%. Since there was only one dataset that employed the *RVFW* method, this may explain the difference in heterogeneity findings between late diastolic strain rate and the other strain and strain rate measures.

Regional Longitudinal Strain Measures—Regional or segmental longitudinal peak systolic strain of the right ventricle is assessed at the apical, mid, and basal ventricular levels of the RV free wall and has been clinically used to assess right ventricle function in both adult and pediatric disease (23,24,31). Five out of the ten eligible datasets in this meta-analysis reported segmental RV strain at all three levels of the right ventricular free wall

(13,16,18–20,23,24). Of theses, 3 datasets used the *Full RV Myocardium* method (16,18–20), and 2 datasets employed the *RVFW* only method (13,23,24) to generate RV segmental longitudinal strain. The meta-analysis demonstrated a significant ($P < 0.05$) base-to-apex gradient for the mean values of normal RV segmental strain (−33.53, −32.33, −29.16, respectively) (Figure 5). Between-study heterogeneity was evidenced by a Cochran's Q statistic ranging from 32.81 to 51.74 ($P < 0.001$) and inconsistency by an I^2 value ranging from 87.8% to 94.5%. The heterogeneity for the segmental strain at the basal and mid-ventricular level of the myocardium was not explained by the different methods, or the age, gender, BSA, heart rate, tissue tracking methodology, frame rate, or probe size; however the heterogeneity at the apical level may be partially explained by the differences in methodology of generating this strain measure, as the I^2 value decreased to 0% for the RVFW only method ($P = 0.662$)

Publication Bias

Both visual inspection of the funnel plot and the non-significant results of the Egger test for the global longitudinal strain measures (p=0.59) suggest the absence of publication bias (figure 6). (26,27) Peak global longitudinal strain (%) was identified in all ten eligible studies for this meta-analysis (26,27).

Sources of Variability

In this meta-analysis age, gender, body surface area, heart rate, frame rate, tissue tracking method, and equipment vendor were tested to determine if any of these parameters influenced the variability in reporting of normal strain and strain rate measures in children (table 2). We modeled this meta-analysis after Yingchoncharoen et al. study on normal left ventricle strain values, but our study also independently assessed equipment-software, probe size, and the number of cardiac cycles stored during acquisition (25). The software tracks myocardial motion through the cardiac cycle, calculating myocardial deformation from echogenic speckles in the B-mode image (12). We specifically included cardiac cycles averaged because most studies report the analysis of three heart cycles, but in a few cases in which cycle length and quality were too different, only two cycles were averaged (12). We also stratified the meta-analysis by the method of generating the strain measurements: *RVFW* only vs. *Full RV myocardium*. Finally, to account for maturational changes in hemodynamic parameters from infancy to adolescence, we also stratified the meta-analysis by age distribution to determine its contribution to the reported ranges of normal values.

To thoroughly examine which parameter might statistically influence the variation in strain measures in this meta-analysis, we performed individual meta-regression analysis on each dependent strain measure and each independent variable. None of the demographic, clinical, or echocardiographic variables were significantly associated with the mean values for any of the seven strain measures (table 4). We could not assess if the blood pressure, or inter vendor-equipment or software were independently associated with the reported variations. The blood pressures were not reported in all of the eligible studies, and each study used a specific General Electric (GE) customized ultrasound scanner (Vivid E7, E9, or I) to acquire the images and specific versions of the GE customized software EchoPAC™ to generate the measures. None of the studies specified race.

Discussion

The right ventricle in children is affected by a wide spectrum of conditions such as chronic lung disease, pulmonary hypertension, sickle cell anemia, asphyxia, patent ductus arteriosous, and congenital and acquired heart disease (12–25,32–34). The RV function may be an important determinant of outcomes for these cardiopulmonary pathologies and the lack of a normal range of values and associated variations is a major impediment to identification of the development of RV dysfunction with strain measures, and its use as a surrogate for the outcomes (11). Thus, defining the normal range of values and their variance is an important step in using them as echocardiographic end points. The main findings of this study are (1) the establishment of a normal range of values of RV global and regional longitudinal strain measures in children on the basis of a meta-analysis, and (2) the evaluation of demographic, clinical, and echocardiographic parameters as potential confounders to the variation in the reported normal values.

This is the second study that we are aware of to use systematic review and meta-analysis to define normal values of strain (25). Yingchoncharoen et al. meta-analysis of normal values of left ventricular strain values introduced meta-analysis statistics into the field of deformation imaging as an invaluable tool for determining normal ranges of strain values and identifying factors that contribute to the reported variations (25). In this study, we evaluated right ventricle global and regional systolic and diastolic deformation parameters in children. We added to this meta-analysis process by: (1) Increasing the search engines from three to five and searching ClinicalTrials.gov to check for ongoing studies related to our topic; (2) Utilizing a trained librarian to create search hedges to cover “concepts” (pediatrics/children, speckle tracking, and right heart ventricles) using phrases harvested from standard word indices and on-topic articles, rather than just using “key terms” to search for articles (Appendix 1); (3) Contacting all the authors of the eligible studies by electronic mail to fill in the missing gaps in data in an attempt to decrease heterogeneity between studies and to publically notify them of the meta-analysis; (4) Independently (by two authors) selecting and reviewing all the eligible studies, and assessing their quality of publication (26–30). Thus, combining our techniques with Yingchoncharoen et al. made this approach more comprehensive and may serve to enhance the field of strain imaging meta-analysis in reporting normal global and regional strain values and identifying the parameters that contribute to the differences in values in adults and children.

Normal ranges of global longitudinal strain measures

This study defines normal values for RV global longitudinal strain (pGLS), global longitudinal systolic (pGLSRs) and diastolic (early, pGLSRe and late, pGLSRa) strain rate. All ten eligible datasets from 13 studies reported normal values of strain measures from small cohorts of healthy children. Except for *The Munich Triathlon Heart Study* (16), which recruited healthy athletes, the other studies recruited healthy children to use as a control population to compare their myocardial deformation parameters to a diseased population in case/control observational study format (12–15,17–24,25). By combining data from all these different studies in a meta-analysis format, this systematic review offers a more

"representative estimate of the range of normal strain values than are possible with individual studies" (25–30).

There is no consensus on which method of generating strain measures is more accurate or correlates more efficiently with health and disease outcomes. Therefore, we stratified our results by the two different methods: (1) *Full RV myocardium*, and (2) *RVFW* only. The meta-analysis, stratified by method of data analysis, demonstrated very narrow mean values for the global strain and strain rate measures (pGLS: −26.54% to −32.98%; pGLSRs −2.2 1/sec to −1.6 1/sec; pGLSRe: 2.0 1/sec to 2.7 1/sec), pGLSRa (1.0 1/sec to 1.3 1/sec). The different methods of generating strain measurements did not explain the heterogeneity in the reporting of different values amongst the studies. Left ventricle global longitudinal strain in healthy children has been reported as lower than RV global longitudinal strain (34–37). In this study, *RV free wall* values of pGLS may be higher than *Full RV myocardium (−30.06% vs. −28.20%)* pGLS values due to the inclusion in the latter of the shared interventricular septum with the left ventricle. However, until further research is done to properly analyze, compare, and correlate each method to different outcomes, in our opinion, both methods are valid approaches as there is a narrow range of the reported mean values between them (Figure 3). The combined normal values for each strain and strain rate measure and their associated ranges are listed in Table 5.

Normal ranges of segmental longitudinal strain measures

The meta-analysis also defined normal ranges for segmental longitudinal strain at the apical, mid basal ventricular levels of the right ventricular free wall (SLS-Apex, SLS-Mid, SLS-Base, respectively). Previous individual studies have demonstrated a base-to-apex segmental longitudinal strain gradient for the RV in children and adults (13,18–20,23,24) and this base-to-apex gradient is reflective in the segmental longitudinal strain meta-analysis (Figure 5). This pattern remains relatively unchanged and may reflect the relative constant geometry of normal heart with maturation. The dominant deep longitudinal layers of the RV are aligned base to apex and allow for greater longitudinal shortening (38–40). Alteration of this normal physiological base-to-apex gradient has the potential to discern clinical changes in myocardial function in patients with different disease processes. The heterogeneity for the segmental longitudinal apical strain only may be partially explained by the different methods of generating this strain measure (figure 7). The normal values for segmental longitudinal strain measures and their associated ranges are listed in Table 5.

Clinical Impact of Normal Strain values

With the knowledge of the range of normal values of RV strain, we strongly feel that these myocardial deformation parameters can now be properly utilized to assess RV function in pathological conditions in children. 2DSTE derived strain measures have already been applied to assess RV function in children with pulmonary hypertension, complex congenital heart defects, sickle cell anemia, and cystic fibrosis (12–24). Hauser et al. also demonstrated the use of strain imaging to assess and track ventricular function in healthy children before and after endurance stress (16). Non-invasive strain imaging of the left ventricle is utilized for monitoring cardiotoxicity of cancer therapeutic drugs in adults and children. It is possible that strain imaging can be used to assess RV function in a similar manner (41) and

in children with primary RV failure or RV failure secondary to left heart conditions to prognosticate the outcomes.

The recommended methods to quantitatively assess RV function in children include tricuspid annular plane systolic excursion (TAPSE), fractional area change (FAC%), and RV myocardial performance index (RV MPI). (1,4,5) In comparison, strain imaging is the only echocardiographic parameter that evaluates both RV systolic and diastolic function at the global and segmental level of the myocardial tissue at the same time (11,42,43). The seven global and segmental strain measures analyzed in this meta-analysis have not all been consistently utilized and reported in clinical practice, however, it is anticipated that by defining the normal ranges and the causes of the reported variation of these strain values, deformation imaging will be used more routinely to assess clinical changes in myocardial function in children. Normal ranges of values may now prove clinically applicable across a broad range of physiologic and pathologic conditions in children.

Source of Bias

The meta-regression in our study showed that the effects of age, gender, HR, body surface area, frame rate, probe size, were not significant determinants of variations among normal ranges of reported strain measurements in children. Yingchoncharoen et al. stated that the lack of explanation of these variables in causing heterogeneity between studies should “not be misconstrued to mean that these features” do not influence strain (25). Yingchoncharoen et al. also observed that changes in systolic blood pressure were independently associated with differences in the reported normal values of strain (25). The mean blood pressures were not documented or described in all 10 eligible studies, precluding its inclusion in the meta-regression or assessment as a cause of heterogeneity. However, future studies that utilize strain as a measure of cardiac function in children should document the blood pressure during the acquisition of the echocardiogram (25).

Age did not explain the between-study heterogeneity of the reported normal ranges of values for peak global longitudinal strain. Colan et al demonstrated that “there are significant age-dependent alterations in myocardial mechanics manifested by a progressive increase in afterload and a reduction in both systolic function and contractility during normal growth and maturation” (44). RV strain changes throughout maturation from infancy to adolescence (36–38). To account for this in reporting normal ranges of values in children, the meta-analysis was stratified by the age distribution in children: pre-puberty (0–9), puberty (10–13), and late adolescents (14–21). The between-study I^2 value remained the same. The normal mean values of pGLS from pre-puberty and puberty stages varied from −24% to −34% with a mean of −29%. By adolescence (14–21 years of age) the pGLS normal ranges varied from −20% to −30% with a lower mean of −26% (Figure 3b). The sample size may not have been adequate to show a statistically significant relationship between RV pGLS and age, but there is a trend in the mean values from infancy to adolescent. Previous work with 2DSTE derived LV pGLS from our group showed a significant relationship between pGLS and age from 0 to 18 years of age that was confirmed by Zhang et. al with three-dimensional speckle tracking echocardiography (3DSTE) derived pGLS (36, 45).

We also intended to discern the role of vendor-specific ultrasound machines and vendor-customized software as a potential confounder to the variation in reported normal values of strain in healthy children, but all of the eligible studies used equipment and software from one manufacturer, General Electric (GE). Yingchoncharoen et al. found that in 28 eligible data sets, only 5 used non-GE equipment, and the use of different vendors was not an explanation of between-study differences in the reported values (25). Recent studies have not demonstrated significant variation between global longitudinal strain measures when different cardiac ultrasound systems were used for imaging acquisition and analysis (46–50). Negishi et al observed that the use of the same specific vendor customized software to generate strain in images acquired from different vendor ultrasound machines showed minimal bias for global longitudinal strain values (47). There were no eligible studies in a control cohort of children that utilized non-GE ultrasound machines or non-GE software to generate right ventricle strain measures. The eligible studies in this meta-analysis used different GE models (GE Vivid E7, E9, I) and different version of the GE EchoPAC™ software (6.0, 6.0.1, 108.1.5, and BT 08) to acquire and generate strain measures. The differences in specific version of GE machines and software platforms did not explain the heterogeneity between the studies and were not significant variables in the meta-regression (Table 3 and Table 4). However, this study cannot necessarily be applied to others using different strain analysis packages, and future studies should look at reproducibility and normal RV longitudinal strain measurements using other packages to validate results for normal values.

Limitations

The meta-analysis of the left ventricle in adults included 2,597 subjects from 24 studies (25). In comparison, there were fewer studies in children that utilized strain imaging to assess RV function. The sample size of 226 patients may be only adequate to detect differences for pGLS and pGLSRs, but not yet for the other strain measurements. As more studies are published, it will be important to continue to update this meta-analysis.

Heterogeneity is more likely to be present in observational studies than randomized control studies (29). All of the eligible studies in this meta-analysis were case-control or observational studies. Heterogeneity is an excepted limitation in meta-analysis when a pooled estimate is the main objective, as is the case with defining normal ranges of values and determining their variations (26–30). However, Yingchoncharoen et al. also demonstrated high heterogeneity, and our study could not identify potential sources (25).

Speckle tracking echocardiography is a semi-automated software analysis program that is computer based, but not user independent: the observer must initially place and then modify tracking region of interests. (51,52). There is a learning curve that is essential before introducing the technique into clinical studies, and it was impossible to assess the level of competence of each echocardiographer and observer who generated the data. The current marker of study quality and reliability is the demonstration and inclusion of reproducibility analysis within each individual study. In this meta-analysis 6/10 data sets individually perform reproducibility analysis with the strain measurements (Appendix 3).

RV global longitudinal strain values are derived only from a single view, making it not a truly global assessment of RV function (42). This meta-analysis pooled two methods that have been employed to generate “global” RV strain in the longitudinal (myocardial deformation directed from the base to the apex) direction. There is a paucity of studies that use radial or circumferential strain measurements in clinical practice to measure cardiac function in children, and those studies have not been able to demonstrate significant reliability. Peak global longitudinal strain remains the most reliable quantitative tool of the three to assess right ventricular function in children in clinical practice (32,33,54).

Peak global longitudinal strain (pGLS) is the peak strain within the systolic period, as defined by the period during which the ventricle is ejecting. In the left ventricle the pGLS within the cardiac cycle occurs before aortic valve closure, and in the right ventricle it occurs before pulmonary valve closure. Post-systolic strain is defined as the total amount of deformation after the valve closure (42). LV post systolic strain has been postulated as a marker of LV ischemia and RV post systolic strain may reflect pathology in the systemic right ventricles (42). Further studies are needed to interpret the RV post systolic values in children.

Conclusions

In normal healthy children, the mean peak global longitudinal strain value is −29.03% (95% CI, −31.52 to −26.54%) mean peak systolic strain rate is −1.88/sec (95% CI, −2.18 to −1.59), mean peak early diastolic strain rate is 2.34 /sec (95% CI, 2.00 to 2.67), and mean peak late diastolic strain rate is 1.18/sec (95% CI, 1.04 to 1.33). A significant base-to-apex gradient of the peak global longitudinal strain in healthy children was observed from the meta-analysis. Variations among different normal ranges do not appear to be dependent on differences in demographic, clinical, or equipment parameters in this meta-analysis. All of the eligible studies used equipment and software from one manufacturer, General Electric (GE).

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Abbreviations

RV	Right Ventricle
RVFW	Right Ventricle free wall
2DSTE	Two-dimensional speckle tracking echocardiography
pGLS	Peak global longitudinal strain
pGLSRs	Peak global longitudinal systolic strain rate
pGLSRe	Peak global longitudinal early diastolic strain rate

pGLSRa	Peak global longitudinal late diastolic strain rate
SLS-Apex	segmental longitudinal apical strain
SLA-Mid	segmental longitudinal mid-ventricular strain
SLS-Base	segmental longitudinal basal strain
I^2	inconsistency index
CI	confidence intervals

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Appendix 1

Electronic data base search hedges

Five search engines were used to identify eligible articles in this review. The search strategies are listed below by their name, results, and date of search.

PubMed (46 results) 5/29/2013

("Heart Ventricles"[Mesh] OR “right ventricle” OR “right ventricles” OR “right ventricle” OR “ventriculus dexter”) AND ("speckle tracking"[All Fields] OR "speckle-tracking"[All Fields] OR "STE-resolution"[All Fields] OR "2D-STE"[All Fields] OR "2DSTE"[All Fields] OR "STE-Derived"[All Fields] OR "2D STE"[All Fields] OR "3D STE"[All Fields] OR "two dimensional STE"[All Fields] OR "Three dimensional STE"[All Fields] OR "2D-strain echocardiography"[All Fields] OR (("Echocardiography"[Mesh] OR "Echocardiography"[All Fields] OR "tracking"[All Fields] OR "imaging"[All Fields]) AND ("speckles"[All Fields] OR "speckle"[All Fields] OR "STE"[tiab]))) AND ("Child"[Mesh] OR "Infant"[Mesh] OR "Adolescent"[Mesh] OR "Pediatrics"[Mesh] OR “Child” OR “Children” OR “Children” OR “toddler” OR “toddlers” OR "Infant" OR “Infants” OR “Newborn Infant” OR “Newborn Infants” OR “Newborns” OR “Newborn” OR “Neonate” OR “Neonates” OR "Adolescent" OR “Adolescents” OR Teen* OR “Youth” OR “Youths”

OR “Adolescence” OR “girl” OR “girls” OR “boy” OR “boys” OR “juvenile” OR “juveniles” OR "Pediatrics" OR “pediatric” OR “pediatry” OR “section 7”) NOT ("Animals"[Mesh] NOT ("Animals"[Mesh] AND "Humans"[Mesh]))

Embase (135 results) 5/29/2013

'heart right ventricle'/exp OR “right ventricle” OR “right ventricles” OR “right ventricle” OR “ventriculus dexter” AND (‘speckle tracking’ OR ‘speckle-tracking’ OR ‘STE-resolution’ OR ‘2D-STE’ OR ‘2DSTE’ OR ‘STE-Derived’ OR ‘2D STE’ OR ‘3D STE’ OR ‘two dimensional STE’ OR ‘Three dimensional STE’ OR ‘2D-strain echocardiography’ OR (('echocardiography'/exp OR ‘Echocardiography’ OR ‘tracking’ OR ‘imaging’) AND (‘speckles’ OR ‘speckle’ OR ‘STE’:ti OR ‘STE’:ab))) AND ('pediatrics'/exp OR 'child'/exp OR 'adolescent'/exp OR ‘Child’ OR ‘Children’ OR ‘Children’ OR ‘toddler’ OR ‘toddlers’ OR ‘Infant’ OR ‘Infants’ OR ‘Newborn Infant’ OR ‘Newborn Infants’ OR ‘Newborns’ OR ‘Newborn’ OR ‘Neonate’ OR ‘Neonates’ OR ‘Adolescent’ OR ‘Adolescents’ OR Teen* OR ‘Youth’ OR ‘Youths’ OR ‘Adolescence’ OR ‘girl’ OR ‘girls’ OR ‘boy’ OR ‘boys’ OR ‘juvenile’ OR ‘juveniles’ OR ‘Pediatrics’ OR ‘pediatric’ OR ‘pediatry’ OR ‘section 7’) NOT ([animals]/lim NOT [humans]/lim)

Scopus (82 results) 5/29/2013

(TITLE-ABS-KEY("Heart Ventricles" OR "right ventricle" OR "right ventricles" OR "right ventricle" OR "ventriculus dexter")) AND (TITLE-ABS-KEY("speckle tracking" OR "speckle-tracking" OR "STE-resolution" OR "2D-STE" OR "2DSTE" OR "STE-Derived" OR "2D STE" OR "3D STE" OR "two dimensional STE" OR "Three dimensional STE" OR "2D-strain echocardiography" OR (("Echocardiography" OR "Echocardiography" OR "tracking" OR "imaging") AND ("speckles" OR "speckle" OR "STE")))) AND (TITLE-ABS-KEY("Child" OR "Infant" OR "Adolescent" OR "Pediatrics" OR "Child" OR "Children" OR "Children" OR "toddler" OR "toddlers" OR "Infant" OR "Infants" OR "Newborn Infant" OR "Newborn Infants" OR "Newborns" OR "Newborn" OR "Neonate" OR "Neonates" OR "Adolescent" OR "Adolescents" OR teen* OR "Youth" OR "Youths" OR "Adolescence" OR "girl" OR "girls" OR "boy" OR "boys" OR "juvenile" OR "juveniles" OR "Pediatrics" OR "pediatric" OR "pediatry" OR "section 7")) AND (LIMIT-TO(EXACTKEYWORD, "Human") OR LIMIT-TO(EXACTKEYWORD, "Humans"))

Cochrane (2 results – CENTRAL) 5/29/2013

("Heart Ventricles" OR “right ventricle” OR “right ventricles” OR “right ventricle” OR “ventriculus dexter”) AND ("speckle tracking" OR "speckle-tracking" OR "STE-resolution" OR "2D-STE" OR "2DSTE" OR "STE-Derived" OR "2D STE" OR "3D STE" OR "two dimensional STE" OR "Three dimensional STE" OR "2D-strain echocardiography" OR (("Echocardiography" OR "Echocardiography" OR "tracking" OR "imaging") AND ("speckles" OR "speckle" OR "STE"))) AND ("Child" OR "Infant" OR "Adolescent" OR "Pediatrics" OR “Child” OR “Children” OR “Children” OR “toddler” OR “toddlers” OR "Infant" OR “Infants” OR “Newborn Infant” OR “Newborn Infants” OR “Newborns” OR “Newborn” OR “Neonate” OR “Neonates” OR "Adolescent" OR “Adolescents” OR Teen* OR “Youth” OR “Youths” OR “Adolescence” OR “girl” OR “girls” OR “boy” OR “boys”

OR “juvenile” OR “juveniles” OR "Pediatrics" OR “pediatric” OR “pediatry” OR “section 7”)

ClinicalTrials.gov **(3 results) 5/29/2013**

("Heart Ventricles" OR “right ventricle” OR “right ventricles” OR “right ventricle” OR “ventriculus dexter”) AND ("speckle tracking") OR "STE-resolution" OR "2D-STE" OR "2DSTE" OR "STE-Derived" OR "2D STE" OR "3D STE" OR "two dimensional STE" OR "Three dimensional STE" OR "2D-strain echocardiography") OR (("Echocardiography" OR "Echocardiography" OR "tracking" OR "imaging") AND ("speckles" OR "speckle" OR "STE"))) AND ("Child" OR "Infant" OR "Adolescent" OR "Pediatrics" OR “Child” OR “Children” OR “Children” OR “toddler” OR “toddlers” OR "Infant" OR “Infants” OR “Newborn Infant” OR “Newborn Infants” OR “Newborns” OR “Newborn” OR “Neonate” OR “Neonates” OR "Adolescent" OR “Adolescents” OR Teen* OR “Youth” OR “Youths” OR “Adolescence” OR “girl” OR “girls” OR “boy” OR “boys” OR “juvenile” OR “juveniles” OR "Pediatrics" OR “pediatric” OR “pediatry” OR “section 7”)

Appendix 2

Qualitative assessment of study reporting

Reporting
Is the objective of the study clearly described?
Are the main outcomes to be measured clearly described?
Are the characteristics of the patients included clearly described in the study?
Are the distributions of principal confounders clearly described?
Are the main findings of the study clearly described?
External validity
Were the subjects asked to participate in the study representative of the entire population?
Internal validity
Was there a clear protocol for generating strain measures?
Was an attempt made to blind those measuring the data to the patient outcomes?
Was an attempt made to blind those acquireing the images to the patient outcomes?
Was reproducibility analysis performed?
Internal validity - confounding (selection bias)
Were the patients cases and controls recruited over the same period of time?

Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions J Epidemiol Community Health 1998;52:377–384.

Appendix 3

Qualitative data for eligible datasets

Study	year	Objective defined?	Outcome described?	Charachteristics described?	Confounders described?	Main findings outlined?	Heterogenous population?	Strain Imaging protocol	Individuals generating data blinded to outcomes?	Sonographers blinded to outcome?	Was reproducbility analysis performed? ****	Case/ controls recruited over same time periods?
Pettersen et al. (21)	2009	Yes	Yes	Yes	Yes	Yes	NS	Yes	No	No	Yes	NS
Koh et al. (17)	2010	Yes	Yes	Yes	Yes	Yes	NS	Yes	No	No	No	NS
Li et al. (18)	2010	yes	yes	yes	yes	yes	NS	Yes	Yes	No	yes	Yes
Sileikiene et al. (22)	2010	yes	yes	yes	yes	yes	NS	Yes	No	No	No	NS
Van Der Hulst et al. * (23,24)	2010	Yes	Yes	Yes	Yes	Yes	NS	Yes	No	No	No	Yes
Dragulescu et al. (13)	2011	Yes	Yes	Yes	Yes	Yes	NS	Yes	No	No	Yes	NS
Blanc et al. (12)	2012	Yes	Yes	Yes	Yes	Yes	NS	Yes	Yes	No	Yes	NS
Friedberg et al. ** (14,15)	2013	yes	yes	yes	yes	yes	NS	Yes	No	No	Yes	Yes
Hauser et al. (16)	2012	Yes	Yes	Yes	Yes	Yes	NS	Yes	NA	NA	No	No
Cua et al. *** (19,20)	2013	Yes	Yes	Yes	Yes	Yes	NS	Yes	Yes	No	Yes	No

Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions J Epidemiol Community Health 1998;52:377–384.

NS, not specified

*
Van Der Hulst AE et al. produced two studies (23,24) that used the same control population, the author recommended using the 2010 study in the analysis (23). The results were the same, but the 2010 study used 19 controls and the 2011 study used 18.

**
Friedberg MK et al. produced two studies (14,15) that used the same control populaiton. Friedberg MK et al. 2012 had 49 controls and Friedberg MK et al. 2013 had 40 controls. The different control numbers were accounted for in the meta-analysis.

***
Cua CL et al is a combination of two studies by Ozcelik et al 2012 (19) and Moiduddin et al 2010 (20), the last author, Cua CL, provided a dataset that combined both studies (n=13 control patients)

****
Each of the studies that performed intra- and inter- observer reproducibility used a combination of Bland Altman analysis, coefficient of variation, and/or intraclass correlation coefficient (ICC). In each study, it was reported that there were either acceptable narrow limits of agreements, coefficient of variation < 15%, and/or ICC > 0.9.

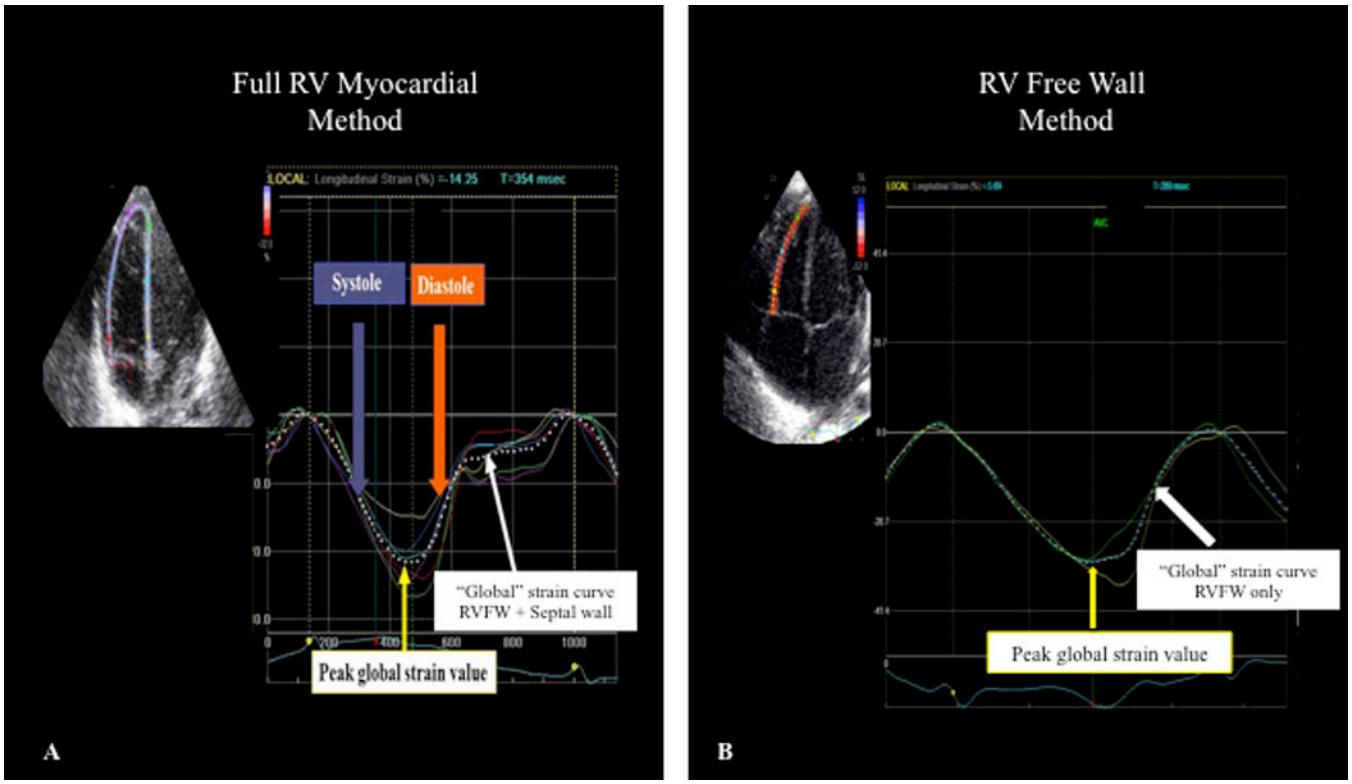


Figure 1.

Right ventricle "Global" longitudinal strain methods of data analysis: *Full RV myocardium method* vs. Right Ventricle Free Wall (*RVFW*) only method. A): *Full RV myocardium:* A region of interest is placed around the entire RV myocardium including the RV free wall and the septal wall. The segmental strain is graphically presented by six different color-code curves and the global longitudinal strain by the white dotted curve. The peak of the average curve of the six segments (the dotted curve) was considered as peak global longitudinal strain (pGLS). B) *RVFW* only : A region of interest is placed around the RVFW only. The basal (yellow), mid (blue), and apical (green) segments of the RV free wall are depicted, as well as the global strain (white dots) of the RV free wall. The peak of the average curve of the 3 segments (the dotted curve) was considered as peak global longitudinal strain (RV pGLS).

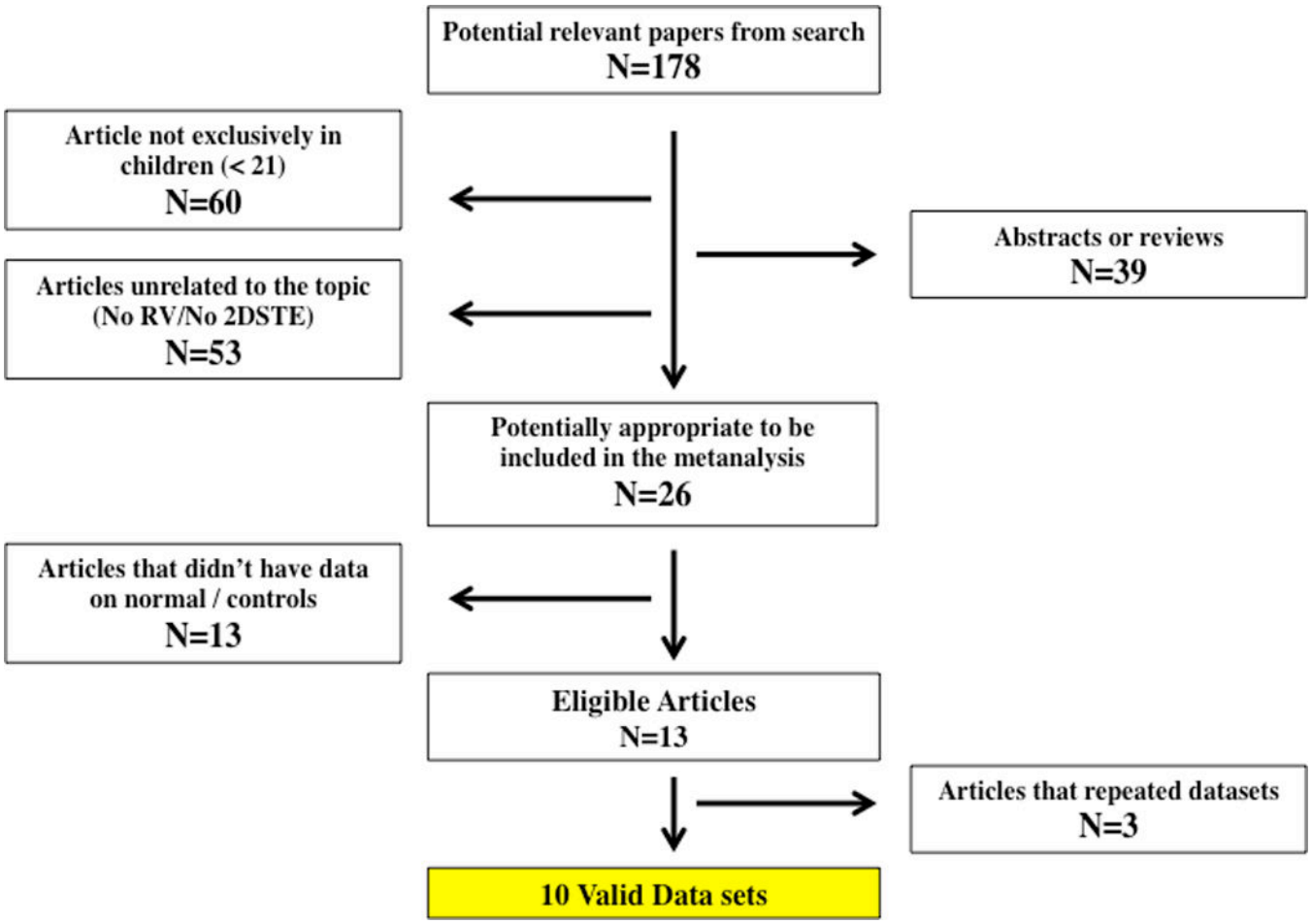
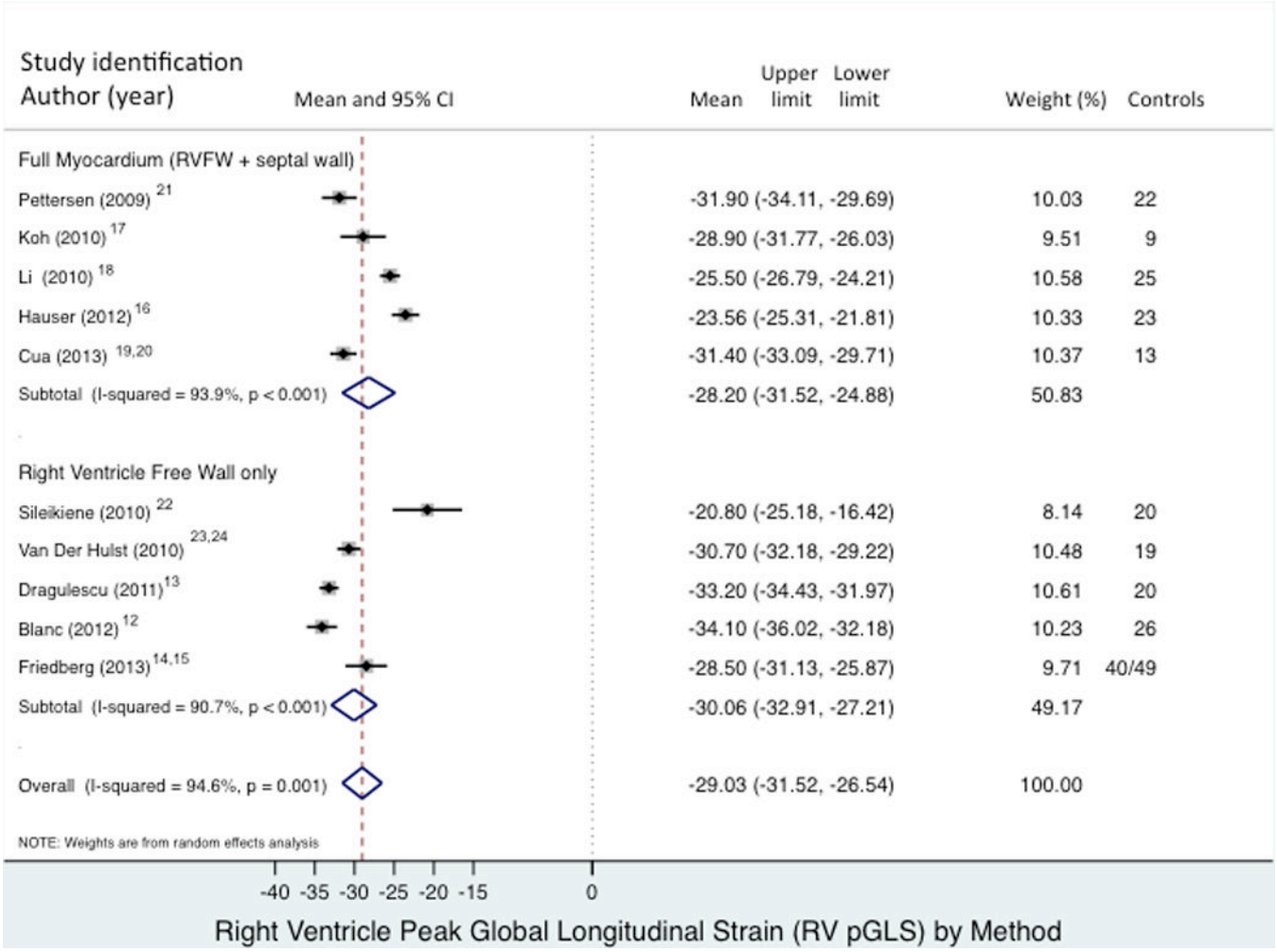


Figure 2.
Process of inclusion of studies in the meta-analysis



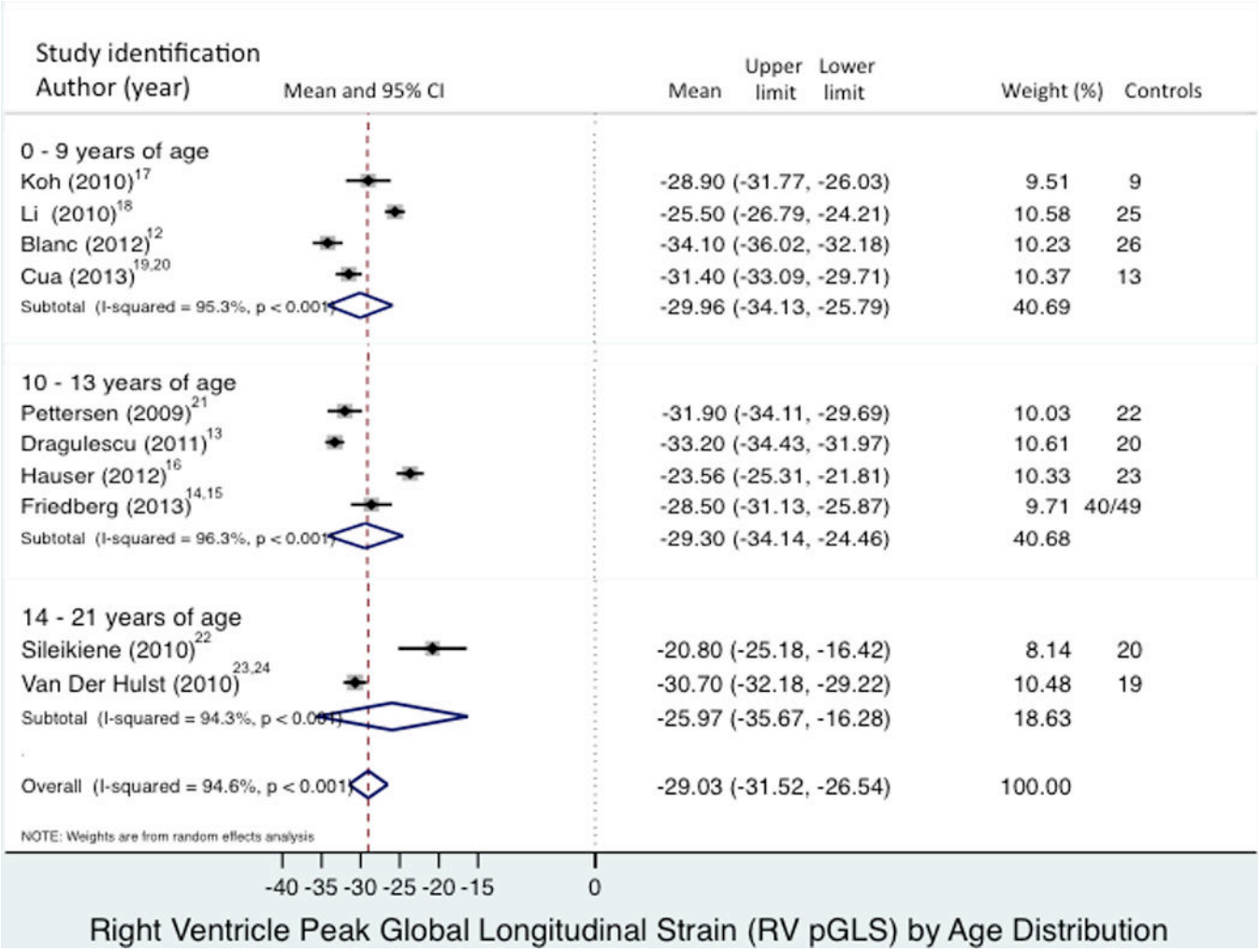


Figure 3.

Normal value of RV pGLS by (A) method of generating RV “global” longitudinal strain and (B) age distribution. The forest plot lists the names of the included studies in chronological order, the mean and confidence intervals with the upper (95%) and lower (5%) limits. Each study is represented by a square that reflects the mean at the point estimate of effect and is proportional to the study's weight in the meta-analysis. A horizontal line extending from either side of the square reflects the 95% confidence interval. The overall meta-analysis measure of effect is plotted as a diamond with the lateral points of the diamond indicating confidence intervals for this mean estimate.

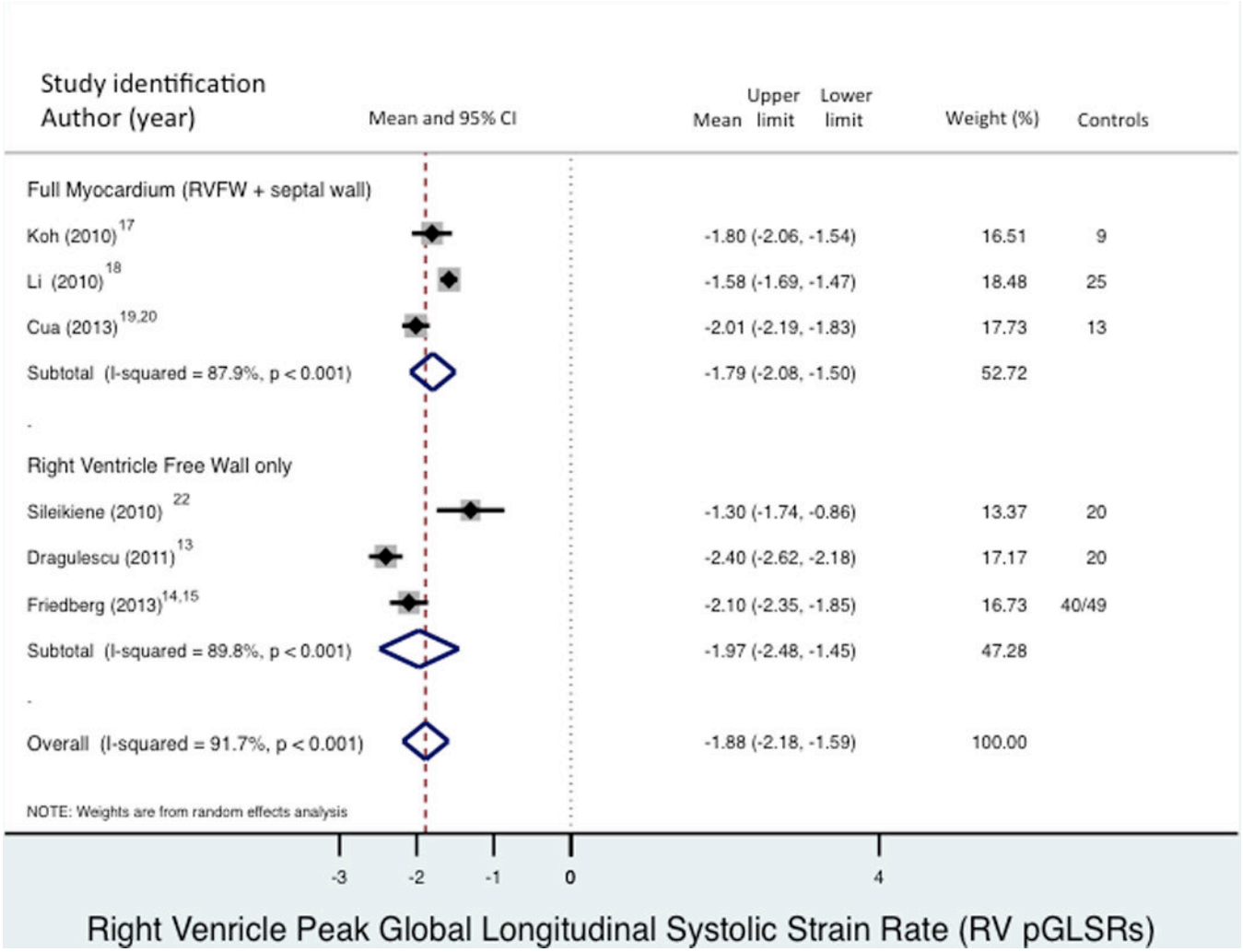


Figure 4.

Normal values of RV global longitudinal systolic strain rate (RV pGLSRs). The forest plot lists the names of the included studies in chronological order, the mean and confidence intervals with the upper (95%) and lower (5%) limits. Each study is represented by a square that reflects the mean at the point estimate of effect and is proportional to the study's weight in the meta-analysis. A horizontal line extending from either side of the square reflects the 95% confidence interval. The overall meta-analysis measure of effect is plotted as a diamond with the lateral points of the diamond indicating confidence intervals for this mean estimate.

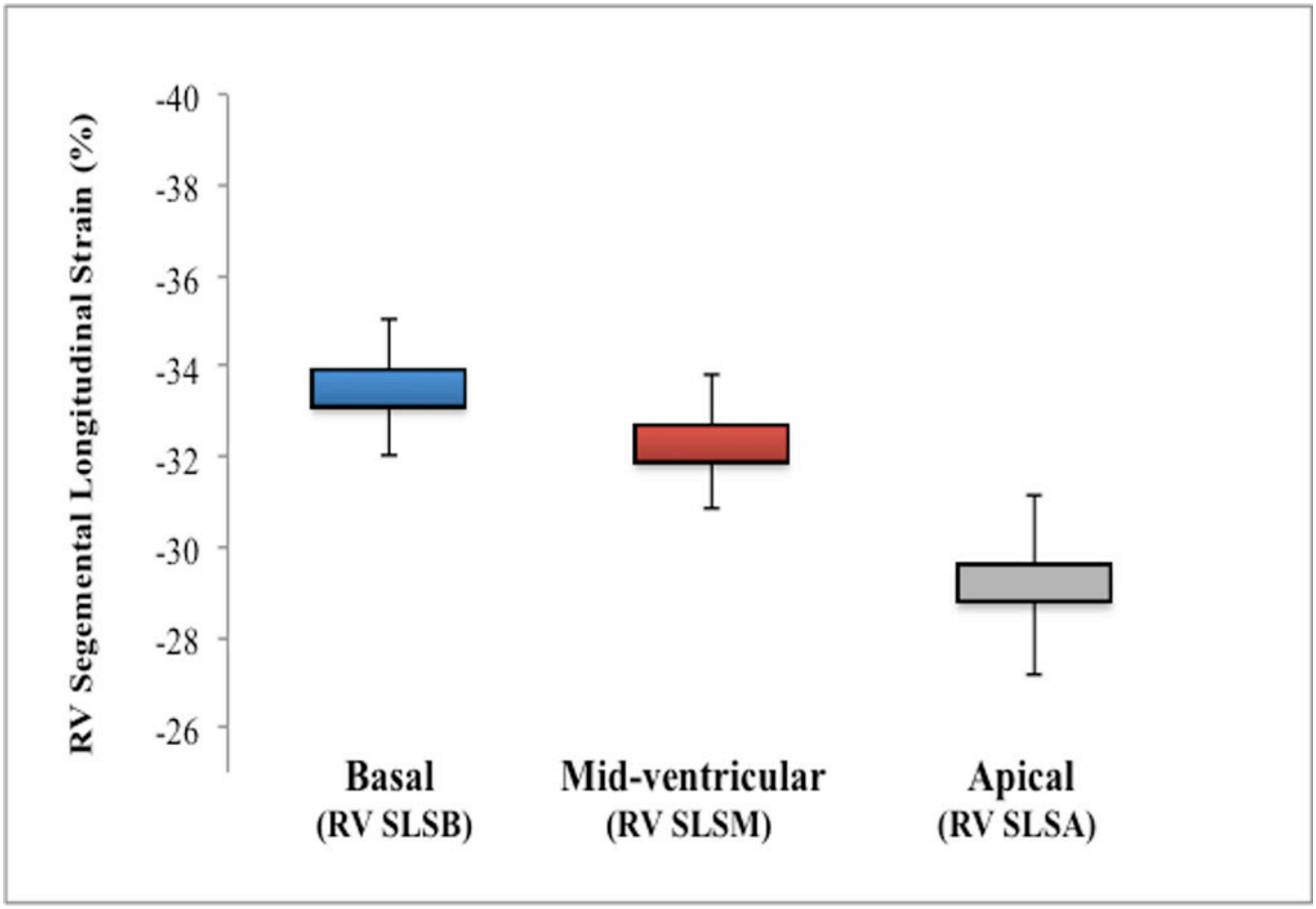


Figure 5.

Normal values of RV Segmental longitudinal strain; a)Apex (RV SLSA); b) mid-ventricular (RV SLSM) c) base (RV SLSB). A significant base-to-apex gradient exists for right ventricle segmental longitudinal strain ($P < 0.05$).

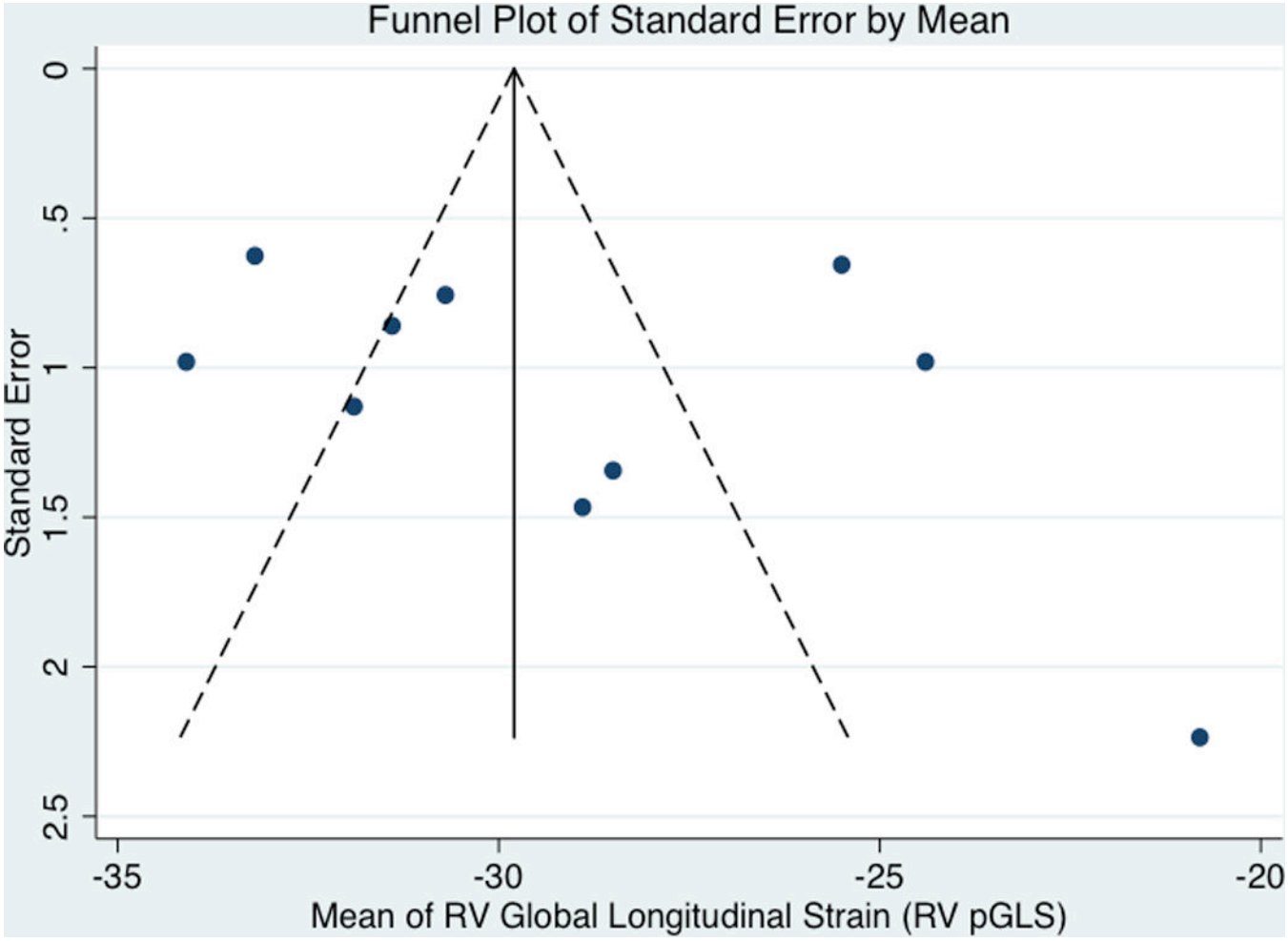


Figure 6.

Publication bias. Funnel plot for studies of right ventricle peak global longitudinal strain (RV pGLS). The standard error of the effect estimate is plotted on the vertical axis. The mean of the RV pGLS is plotted on the horizontal axis. Visual inspection shows symmetry in the distribution of the studies that suggests the absence of publication bias (P=0.59 from the Egger test for statistical funnel plot symmetry).

Table 1

Study descriptions and patient characteristics

Study	year	n	mean age (y)	Male	Female	HR	BSA	RV Global Strain	RV Segemental Strain	RV Global Strain Rate	Control Selection	Disease Studied
Pettersen et al. (21)	2009	22	12.7	14.0	8.0	NS	1.44 ± 0.24	Yes	No	No	Normal Controls	TGA
Koh et al. (17)	2010	9	5.5	6.0	3.0	NS	0.81 ± 0.44	Yes	No	Yes	Normal Controls	LVNC
Li et al. (18)	2010	25	5.7	16.0	9.0	94 ± 18	NS	Yes	Yes	Yes	Normal Controls	TOF
Sileikiene et al. (22)	2010	20	16.3	10.0	10.0	NS	NS	Yes	Yes	Yes	Normal Controls	AV node ablation
Van Der Hulst et al.* (23,24)	2010	19	14.1	12.0	7.0	69 ± 13	1.6 ± 0.3	Yes	Yes	No	Normal Controls	TOF
Dragulescu et al. (13)	2011	20	12.0	11.0	9.0	73 ± 12	1.42 ± 0.29	Yes	Yes	Yes	Normal Controls	TOF/ASD
Blanc et al. (12)	2012	26	8.8	21.0	8.0	79 ± 11	1.07 ± 0.27	Yes	No	No	Normal Controls	Sickle Cell Anemia
Friedberg et al.** (14,15)	2013	40/49	12.0	NS	NS	NS	NS	Yes	No	Yes	Normal Controls	ToF
Hauser et al. (16)	2012	23	12.7	5.0	18.0	70 ± 10	NS	Yes	Yes	No	Athletes	
Cua et al.*** (19,20)	2013	13	5.7	NS	NS	88 ± 11	NS	Yes	Yes	Yes	Normal Controls	TOF, CF

HR, heart rare; BSA, body surface area; RV, right ventricle

TGA, transpostion of the great arteries; LVNC, left ventricular non-compaction; TOF, tetralogy of fallot; CF, cystic fibrosis; AV, aortic valve

NS, not specified

* Van Der Hulst AE et al. produced two studies (23,24) that used the same control population, the author recommended using the 2010 study in the analysis (23). The results were the same, but the 2010 study used 19 controls and the 2011 study used 18.

** Friedberg MK et al. produced two studies (14,15) that used the same control populaiton. Friedberg MK et al. 2012 had 49 controls and Friedberg MK et al. 2013 had 40 controls. The different control numbers were accounted for in the meta-analysis.

*** Cua CL et al is a combination of two studies by Ozcelik et al 2012 (19) and Moiduddin et al 2010 (20), the last author, Cua CL, provided a dataset that combined both studies (n=13 control patients)

Table 2

Echocardiographic characteristics

Study	Year	n	Vendor	Software	view	Probe(MHz)	Cardiac cycles	FR (frames/second)	Tissue Tracking
Pettersen et al. (21)	2009	22	GE EP Vivid 7	EP	Apical 4CH	NS	3	69–112	Endomyocardial
Koh et al. (17)	2010	9	GE EP Vivid 7	EP	Apical 4CH	4.4 – 10	3	60–80	NS
Li et al. (18)	2010	25	GE EP Vivid 7	EP 6.0	Apical 4CH	3–7	3	60–90	Endomyocardial
Sileikiene et al. (22)	2010	20	GE EP Vivid 7	EP	Apical 4CH	3.0	NS	40–70	Endomyocardial
Van Der Hulst et al.* (23,24)	2010	19	GE EP Vivid 7	EP 108.1.5	Apical 4CH	3.5	3	40–70	Endomyocardial
Dragulescu et al. (13)	2011	20	GE EP Vivid 7/9	EP 110.1.3	Apical 4CH	NS	3	50–100	Endomyocardial
Blanc et al. (12)	2012	26	GE EP Vivid 7	EP 6.0.1	Apical 4CH	5.0	3	70–100	Endomyocardial
Friedberg et al.** (14,15)	2013	40/49	GE EP Vivid 7	EP BT 08	Apical 4CH	4–10	3	60–90	Endomyocardial
Hauser et al. (16)	2012	23	GE EP Vivid 7	EP 6.0.1	Apical 4CH	4–10	3	60–90	NS
Cua et al.*** (19,20)	2013	13	GE EP Vivid 7/I	EP 6	Apical 4CH	5–7	3	86	Epi-endocardial

GE, General Electric; EP, EchoPAC; 4CH, 4-chamber; FR, frame rate
NS, not specified

Tissue tracking methodology: Endomyocardial and epicardial-endocardial. The endocardial border was drawn manually and thickness of the region of interest adjusted to cover the myocardium but excluded the pericardium.

* Van Der Hulst AE et al. produced two studies (23,24) that used the same control population, the author recommended using the 2010 study in the analysis (23). The results were the same, but the 2010 study used 19 controls and the 2011 study used 18.

** Friedberg MK et al. produced two studies (14,15) that used the same control populaiton. Friedberg MK et al. 2012 had 49 controls and Friedberg MK et al. 2013 had 40 controls. The different control numbers were accounted for in the meta-analysis.

*** Cua CL et al is a combination of two studies by Ozcelik et al 2012 (19) and Moiduddin et al 2010 (20), the last author, Cua CL, provided a dataset that combined both studies (n=13 control patients)

Table 3

Meta-regression results for global longitudinal strain (pGLS)

	b (95% CI)	P
Age	0.17 (−0.68 to 1.01)	0.66
Male Gender	−0.33 (−1.29 to 0.63)	0.44
HR	−0.36 (−0.78 to 0.06)	0.21
BSA	−1.21 (−12.78 to 10.36)	0.76
Frame Rate	−0.11 (−0.33 to 0.11)	0.27
Ultrasound Scanner	−3.44 (−10.25 to 3.37)	0.28
Vendor Software	0.76 (−0.91 to 2.42)	0.33
Probe Size	−3.21(−7.50 to 1.08)	0.11
Tissue tracking	0.56 (−0.71 to 1.42)	0.53

Table 4

Meta-regression results for right ventricle global and segmental strain

	P value (pGLSRs)	P value (pGLSRe)	P value (pGLSRa)	P value (SLS-Apex)	P value (SLS-Mid)	P value (SLS-Base)
Age	0.93	0.38	0.19	0.60	0.60	0.08
Male Gender	0.88	0.73	0.89	0.19	0.19	0.42
HR	0.16	NA	NA	0.38	0.38	0.43
BSA	NA	NA	NA	NA	NA	NA
Frame Rate	0.61	0.22	0.22	0.90	0.89	0.10
Ultrasound Scanner*	0.10	0.61	0.47	0.43	0.14	0.19
Vendor Software*	0.14	0.35	0.39	0.94	0.94	0.40
Probe Size	0.18	0.11	0.24	0.46	0.46	0.26
Tissue Tracking	0.34	0.65	0.47	0.76	0.94	0.52

NA, not analyzed because there were not enouch variables

pGLSRs, peak global longitudinal systolic strain rate; pGLSRe, peak global longitudinal early diasotlic strain rate, pGLSRe,

*All of the eligible studies in this meta-analysis used machines and software from one manufacturer (GE). In our study different models of GE machines (GE Vivid E7, E9, I) and different version of the GE EchoPAC software (6.0, 6.01., 108.1.5, and BT 08) were employed in the image acquisition and data analysis.

Table 5

Normal right ventricle global and segmental longitudinal strain means values

	Mean	Upper 95% limit	Lower 5% limit
Global Longitudinal Strain Measures*			
RV global strain (pGLS)	−29.03%	−31.52%	−26.54%
RV systolic strain rate (pGLSRs)	−1.88	−2.18	−1.59
RV early diastolic strain rate (pGLSRe)	2.34	2.00	2.67
RV late diasotlic strain rate (pGLSRa)	1.18	1.04	1.33
Segmental Longitudinal Strain measures			
RV segemental apical strain (SLS-Apex)	−29.16%	−32.99%	−25.33%
RV segmental mid-ventricular strain (SLS-Mid)	−32.33%	−35.42%	−29.24%
RV segmental basal strain (SLS-Base)	−33.53%	−37.64%	−29.42%

* These normal values represent the the combined normal values from the two methods used to generate the "global" strain; (1) *Full RV Myocardium; (2) RV Free Wall* only Strain (%), Strain Rate (1/sec)