

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

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**Background:** Establishment of the range of normal values and associated variations of two-dimensional (2D) speckle-tracking echocardiography (STE)-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 2D STE in children and to identify confounders that may contribute to differences in reported measures.

**Methods:** A systematic review was conducted in PubMed, Embase, Scopus, the Cochrane Central Register of Controlled Trials, and [ClinicalTrials.gov](http://ClinicalTrials.gov). Search hedges were created to cover the concepts of pediatrics, STE, and the right heart ventricle. Two investigators independently identified and included studies if they reported the 2D STE-derived RV strain measure RV peak global longitudinal strain, peak global longitudinal systolic strain rate, peak global longitudinal early diastolic strain rate, peak global longitudinal late diastolic strain rate, or segmental longitudinal strain at the apical, middle, and basal ventricular levels in healthy children. Quality and reporting of the studies were assessed. The weighted mean was estimated using random effects with 95% confidence intervals (CIs), heterogeneity was assessed using Cochran's Q statistic and the inconsistency index ( $I^2$ ), and publication bias was evaluated using funnel plots and Egger's test. Effects of demographic, clinical, equipment, and software variables were assessed in a metaregression.

**Results:** The search identified 226 children from 10 studies. The reported normal mean values of peak global longitudinal strain among the studies varied from  $-20.80\%$  to  $-34.10\%$  (mean,  $-29.03\%$ ; 95% CI,  $-31.52\%$  to  $-26.54\%$ ), peak global longitudinal systolic strain rate varied from  $-1.30$  to  $-2.40 \text{ sec}^{-1}$  (mean,  $-1.88 \text{ sec}^{-1}$ ; 95% CI,  $-2.10$  to  $-1.59 \text{ sec}^{-1}$ ), peak global longitudinal early diastolic strain rate ranged from  $1.7$  to  $2.69 \text{ sec}^{-1}$  (mean,  $2.34 \text{ sec}^{-1}$ ; 95% CI,  $2.00$  to  $2.67 \text{ sec}^{-1}$ ), and peak global longitudinal late diastolic strain rate ranged from  $1.00$  to  $1.30 \text{ sec}^{-1}$  (mean,  $1.18 \text{ sec}^{-1}$ ; 95% CI,  $1.04$  to  $1.33 \text{ sec}^{-1}$ ). A significant base-to-apex segmental strain gradient ( $P < .05$ ) was observed in the RV free wall. There was significant between-study heterogeneity and inconsistency ( $I^2 > 88\%$  and  $P < .01$  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 metaregression showed that these effects were not significant determinants of variations among normal ranges of strain values. There was no evidence of publication bias ( $P = .59$ ).

**Conclusions:** This study is the first to define normal values of 2D STE-derived RV 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  $-1.88 \text{ sec}^{-1}$  (95% CI,  $-2.10$  to  $-1.59 \text{ sec}^{-1}$ ). RV segmental strain has a stable base-to-apex gradient that highlights the dominance of deep longitudinal layers of the right ventricle that are aligned base to apex. Variations among different normal ranges did 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 (GE Healthcare). (*J Am Soc Echocardiogr* 2014;27:549-60.)

**Keywords:** Right ventricle, Cardiac function, Global longitudinal strain, Speckle-tracking echocardiography, Children

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**Abbreviations****BSA** = Body surface area**CI** = Confidence interval**HR** = Heart rate**pGLS** = Peak global longitudinal strain**pGLSRa** = Peak global longitudinal late diastolic strain rate**pGLSR<sub>e</sub>** = Peak global longitudinal early diastolic strain rate**pGLSR<sub>s</sub>** = Peak global longitudinal systolic strain rate**RV** = Right ventricular**RVFW** = Right ventricular free wall**STE** = Speckle-tracking echocardiography**2D** = Two-dimensional

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

The use of myocardial strain parameters derived from 2D STE to measure RV function in children requires knowledge of the range of normal values.<sup>11</sup> 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.<sup>12-24</sup> 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.<sup>11</sup>

There are several potential sources of variation among the reported values in studies that may influence the acquisition and generation of strain measures, specifically patient demographics (age, gender, race), clinical factors (heart rate [HR], blood pressure, weight, body surface area [BSA]), and equipment and image technique variables (ultrasound and vendor-customized software, probe size, tissue-tracking methodology, and frame rate).<sup>25</sup> Similar to Yingchoncharoen *et al*.<sup>25</sup> 2012 meta-analysis of the normal ranges of left ventricular strain in adults, we sought to define a range of normal RV strain measures using a compilation of all studies that reported values for cohorts of normal or control children. The objectives of our study were to perform a meta-analysis of normal ranges of RV longitudinal strain and strain rate measurements derived from 2D STE in children and to identify confounders that may contribute to differences and variability in reported measures.

**METHODS****Search Strategy and Protocol**

S.F., our librarian trained in systematic reviews, created search hedges to cover the concepts of pediatrics or children, STE, and the right heart ventricle using terms harvested from standard term indices and on-topic articles (Appendix 1; available at [www.onlinejase.com](http://www.onlinejase.com)). To exclude animals, S.F. used the human filter for PubMed, recommended in the *Cochrane Handbook for Systematic Reviews of Interventions*,

and then used that as a model to create similar filters for the other searched databases.<sup>26</sup> The search strategy was conducted in PubMed, Embase, Scopus, the Cochrane Central Register of Controlled Trials, and [ClinicalTrials.gov](http://ClinicalTrials.gov). Searches were completed by May 2013.

**Study Selection and Eligibility Criteria**

Studies were included if the articles reported using strain derived from 2D STE to measure RV function in healthy pediatric normal or control subjects. Studies that exclusively included children aged <21 years 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.<sup>12-24</sup>

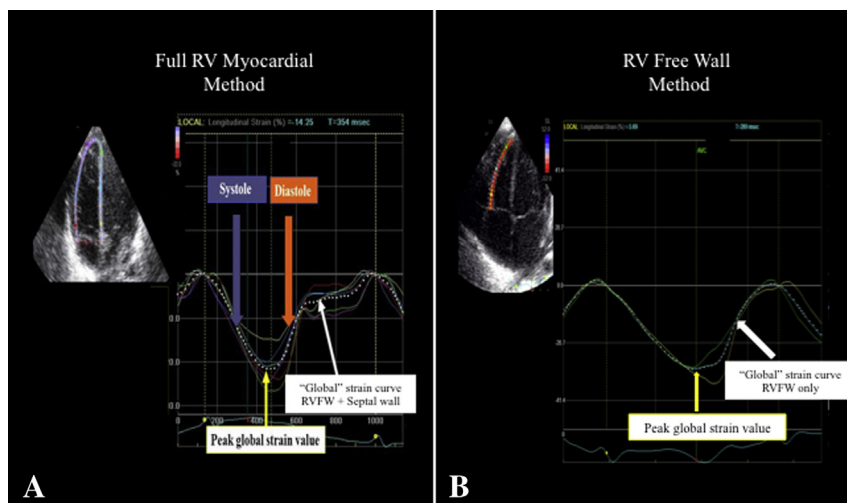
Seven specific global and segmental strain and strain rate measurements were included in the meta-analysis. The global longitudinal strain measures included (1) peak global longitudinal strain (pGLS) within the systolic period, (2) peak global longitudinal systolic strain rate (pGLSR<sub>s</sub>), (3) peak global longitudinal early diastolic strain rate (pGLSR<sub>e</sub>), and (4) peak global longitudinal late diastolic strain rate (pGLSR<sub>a</sub>). The segmental longitudinal strain measures included segmental longitudinal strain at the (5) apex, (7) middle, and (7) basal ventricular levels of the RV free wall (RVFW). Studies were excluded from this analysis if they were abstracts only without full text or review articles.<sup>25</sup> All echocardiographic strain measurements were 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). In method 1 (full RV myocardium), global longitudinal myocardial deformation can be calculated on the basis of the entire traced contour of the right ventricle, which includes the RVFW and the septal wall.<sup>21</sup> In method 2 (RVFW), the weighted average of the three regional values of the lateral RVFW only (basal, middle, and apical segments) provides the value of global longitudinal RV strain.<sup>23,24</sup> (Figure 1). We stratified our meta-analysis by the "full RV myocardium" versus "RVFW only" methods of reporting "global" RV strain and strain rate to account for the different techniques used among 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 were extracted and entered into an electronic database: (1) study (first and last authors and year of publication), (2) demographics (number of control subjects, age, and gender), (3) clinical (HR and 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 authors of the eligible studies<sup>12-24</sup> were contacted by e-mail to notify them of the meta-analysis and to 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, on the basis of the quality assessment methodology of Downs *et al*.<sup>27</sup> (Appendix 2; available at [www.onlinejase.com](http://www.onlinejase.com)). 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



**Figure 1** RV “global” longitudinal strain methods of data analysis: full RV myocardium method versus RVFW-only method. **(A)** Full RV myocardium: A region of interest is placed around the entire RV myocardium, including the RVFW and the septal wall. Segmental strain is graphically presented by six different color-coded curves and global longitudinal strain by the white dotted curve. The peak of the average curve of the six segments (*the dotted curve*) was considered pGLS. **(B)** RVFW only: A region of interest is placed around the RVFW only. The basal (*yellow*), middle (*blue*), and apical (*green*) segments of the RVFW are depicted, as well as the global strain (*white dots*) of the RVFW. The peak of the average curve of the three segments (*the dotted curve*) was considered pGLS.

validation for each study. For strain imaging, we postulated that the most important quality assessment parameters are related to (1) study documentation of intraobserver and interobserver reproducibility of strain measurements, (2) documentation of patient blood pressure and HR, (3) blinding to patient outcomes of the individuals acquiring the images and the observers generating the measures, and (4) a protocol for image acquisition and data analysis.

### Statistical Analysis and Data Synthesis

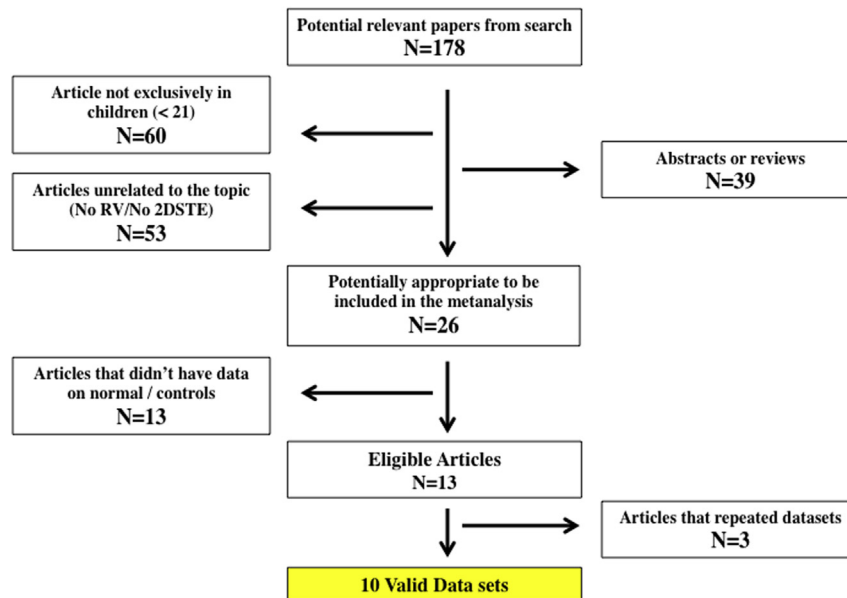
Meta-analysis was performed using Stata version IC 12 (StataCorp LP, College Station, TX). The means and 95% confidence intervals (CI) of strain measures were computed using random-effects models weighted by inverse variance. Between-study statistical heterogeneity was assessed using Cochran’s  $Q$  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 the results of individual studies and meta-analyses.<sup>26-30</sup> The forest plot was used as a graphical display of the relative strengths of the effect estimates and CIs for each of the individual studies and the entire meta-analysis.<sup>26-30</sup> A forest plot is presented with five columns. The left-hand column lists the names of the included studies in chronologic order. 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 4). A horizontal line extending from either side of the square reflects the 95% CI. The overall meta-analysis measure of effect is plotted as a diamond, with the lateral points of the diamond indicating CIs 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. The third column lists the mean value for each study with upper (95%) and lower (5%) limits. The fourth column lists the study weights. Finally, the fifth column lists the number of subjects in each study.<sup>26-30</sup>

Publication bias was assessed using funnel plots and Egger’s test. A funnel plot is a scatterplot of the effect estimates from individual studies against a measure of each study’s size.<sup>26,27</sup> It is a qualitative visual assessment used 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 center-line, and small studies will be on both sides of the average. A symmetric distribution of studies in the funnel plot suggests the absence of publication bias.<sup>26,27</sup> However, visual interpretation of a funnel plot may be too subjective because statistical power is determined by factors in addition to sample size.<sup>26</sup> The funnel plot was therefore combined with Egger’s 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.<sup>26</sup> Finally, there are a number of important variables that may influence the differences in the reported strain measures among studies,<sup>25</sup> and the source of these variations was sought between studies using metaregression to estimate the percentage of heterogeneity on the influence of the variation in normal strain measurements.<sup>28-30</sup>

## RESULTS

### Eligibility Criteria

An initial search identified 268 articles. After excluding duplicates and triplicates ( $n = 90$ ), 178 studies were screened for relevance. Studies not exclusively including children ( $n = 60$ ), those unrelated to the topics ( $n = 53$ ), abstracts without text or reviews ( $n = 39$ ), and reports that had no data on controls or normal children ( $n = 13$ ) were then excluded. Searching the reference lists of retrieved reports did not reveal any additional results. No ongoing studies were found in the clinical trials registries. Thirteen published observational or case-control studies met the inclusion criteria (Figure 2). Three sets of studies used overlapping control population data sets.<sup>14,15,19,20,23,24</sup> The first or last author of each of these studies



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

was contacted by e-mail, and one control data set was either provided or chosen on the basis of author recommendation (Tables 1 and 2). In total, 10 data sets of strain measures from 13 studies of strain measures with 226 children were considered eligible for assessment in the meta-analysis (Figure 2). All studies that met the search criteria were in English, although the search criteria were not limited to English-language reports.

### Study Selection on the Basis of Strain Measures

All 10 data sets (13 articles) with 226 patients were eligible for the meta-analysis of pGLS.<sup>12-24</sup> From the 10 data sets, six data sets with 136 patients reported pGLSRs and were included in the meta-analysis of pGLSRs,<sup>13-15,17-20,22</sup> five data sets with 116 patients were eligible for the meta-analysis of pGLSRs,<sup>14,15,17-20,22</sup> and four data sets with 67 patients were eligible for the meta-analysis of pGLSRa.<sup>17-20,22</sup> In addition, from the 10 data sets, five data sets with 100 patients reported segmental strain measures at the apical, middle, and basal ventricular levels of the RVFW and were analyzed in the meta-analysis of segmental strain.<sup>13,16,18-20,23,24</sup> 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 studies included (Appendices 2 and 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, but they did not all document blood pressure. All studies used detailed strain image acquisition and data-processing protocols. None of the studies clearly stated how many echocardiographers acquired the images and their training levels with regard to 2D speckle-tracking echocardiographic image acquisition. Only a few studies specified how many individuals performed the data analysis and if they were blinded to patient outcomes.<sup>12,18-20</sup> Intraobserver and interobserver reproducibility

analysis was performed in six of 10 data sets<sup>12-15,18-21</sup> and referenced in three of 10.<sup>17,22-24</sup>

### Normal Ranges

**Global Longitudinal Strain Measures.** *pGLS.*—We stratified the meta-analysis by the full RV myocardium versus RVFW-only method of reporting “global” RV strain and strain rate to account for the different techniques used among studies. Of the 10 eligible data sets in this meta-analysis, five used the full RV myocardium method,<sup>16-21</sup> and five used the RVFW-only method<sup>12-15,22-24</sup> when reporting normal values for “global” longitudinal RV strain. Normal mean values of pGLS for all 10 data sets 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 ( $P < .0001$ ) 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, HR, 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 pGLS.**—Age did not explain the heterogeneity of the reported normal ranges of values for pGLS. The breakdown of the age distribution for the studies was as follows: four data sets included patients aged 0 to 9 years,<sup>12,17-20</sup> four data sets included patients aged 10 to 13 years,<sup>13-16</sup> and two data sets included patients aged 14 to 21 years.<sup>22-24</sup> 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 years). Cochran’s Q statistic ranged from 17.59 to 82.13 ( $P < .0001$ ), and the  $I^2$  value remained the same for both methods, ranging from 93.9% to 95.1% (Figure 3B).



**Table 1** Study descriptions and patient characteristics

Study	Year	n	Mean age (y)	Male (%)	Female (%)	HR (beats/min), mean $\pm$ SD	BSA (m <sup>2</sup> ), mean $\pm$ SD	RV global strain	RV segmental strain	RV global strain rate	Control selection	Disease studied
Petersen <i>et al.</i> <sup>21</sup>	2009	22	12.7	14.0	8.0	NS	1.44 $\pm$ 0.24	Yes	No	No	Normal controls	TGA
Koh <i>et al.</i> <sup>17</sup>	2010	9	5.5	6.0	3.0	NS	0.81 $\pm$ 0.44	Yes	No	Yes	Normal controls	LUNC
Li <i>et al.</i> <sup>18</sup>	2010	25	5.7	16.0	9.0	94 $\pm$ 18	NS	Yes	Yes	Yes	Normal controls	ToF
Sileikiene <i>et al.</i> <sup>22</sup>	2010	20	16.3	10.0	10.0	NS	NS	Yes	Yes	Yes	Normal controls	AV node ablation
Van der Hulst <i>et al.</i> <sup>23,24,*</sup>	2010	19	14.1	12.0	7.0	69 $\pm$ 13	1.6 $\pm$ 0.3	Yes	Yes	No	Normal controls	ToF
Dragulescu <i>et al.</i> <sup>13</sup>	2011	20	12.0	11.0	9.0	73 $\pm$ 12	1.42 $\pm$ 0.29	Yes	Yes	Yes	Normal controls	ToF/ASD
Blanc <i>et al.</i> <sup>12</sup>	2012	26	8.8	21.0	8.0	79 $\pm$ 11	1.07 $\pm$ 0.27	Yes	No	No	Normal controls	Sickle-cell anemia
Friedberg <i>et al.</i> <sup>14,15,†</sup>	2013	40/49	12.0	NS	NS	NS	NS	Yes	No	Yes	Normal controls	ToF
Hauser <i>et al.</i> <sup>16</sup>	2012	23	12.7	5.0	18.0	70 $\pm$ 10	NS	Yes	Yes	No	Athletes	ToF, CF
Cua <i>et al.</i> <sup>19,20,‡</sup>	2013	13	5.7	NS	NS	88 $\pm$ 11	NS	Yes	Yes	Yes	Normal controls	ToF, CF

AV, Aortic valve; CF, cystic fibrosis; LUNC, left ventricular noncompaction; NS, not specified; TGA, transposition of the great arteries; ToF, tetralogy of Fallot.

\*Van der Hulst *et al.* produced two studies<sup>23,24</sup> that used the same control population; the author recommended using the 2010 study in the analysis.<sup>23</sup> The results were the same, but the 2010 study used 19 controls and the 2011 study used 18.

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

‡Cua *et al.* is a combination of two studies by Moiduddin *et al.* (2010)<sup>19</sup> Ozcelik *et al.* (2012)<sup>20</sup>; the last author provided a data set that combined both studies ( $n = 13$  control patients).

**pGLSRs.**—Six of the 10 eligible data sets reported pGLSRs.<sup>13-15,17-20,22</sup> Of these six data sets, three used the full RV myocardium method<sup>17-20</sup> and three used the RVFW-only method.<sup>13-15,22</sup> Normal mean values of pGLSRs for all six data sets combined varied from  $-1.30$  to  $-2.40$  sec<sup>-1</sup> (mean,  $-1.88$  sec<sup>-1</sup>; 95% CI,  $-2.18\%$  to  $-1.59$  sec<sup>-1</sup>). Between-study heterogeneity was evidenced by a Cochran's Q statistic of 59.2 ( $P < .0001$ ) 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, HR, tissue-tracking methodology, frame rate, or probe size. Normal mean values of pGLSRs for the RVFW method ranged from  $-1.58$  to  $-2.01$  sec<sup>-1</sup> (mean,  $-1.79$  sec<sup>-1</sup>; 95% CI,  $-2.08$  to  $-1.50$  sec<sup>-1</sup>). Normal mean values for pGLSRs for the full RV myocardium method ranged from  $-1.30$  to  $-2.40$  sec<sup>-1</sup> (mean,  $-1.97$  sec<sup>-1</sup>; 95% CI,  $-2.48$  to  $-1.45$  sec<sup>-1</sup>) (Figure 4).

**pGLSRsRe.**—Five of the 10 eligible data sets reported pGLSRsRe.<sup>14,15,17-20,22</sup> Of these five, three used the full RV myocardium method,<sup>17-20</sup> and two studies used the RVFW-only method.<sup>14,15,22</sup> Normal mean values of pGLSRsRe for all five data sets combined varied from  $1.70$  to  $2.69$  sec<sup>-1</sup> (mean,  $2.34$  sec<sup>-1</sup>; 95% CI,  $2.00$ – $2.67$  sec<sup>-1</sup>). Between-study heterogeneity was evidenced by a Cochran's Q statistic of 29.4 ( $P < .0001$ ) and inconsistency by an  $I^2$  value of 86.4%. The heterogeneity was not explained by different techniques (full RV myocardium vs RVFW only) to acquire pGLSRsRe. In addition, the heterogeneity was not explained by age, gender, BSA, HR, tissue-tracking methodology, frame rate, or probe size. Normal values of pGLSRs for the RVFW method ranged from  $2.12$  to  $2.60$  sec<sup>-1</sup> (mean,  $2.40$  sec<sup>-1</sup>; 95% CI,  $2.06$ – $2.74$  sec<sup>-1</sup>). Normal values for pGLSRs for the full RV myocardium method ranged from  $1.70$  to  $2.69$  sec<sup>-1</sup> (mean,  $2.20$  sec<sup>-1</sup>; 95% CI,  $1.23$ – $3.17$  sec<sup>-1</sup>)

**pGLSRa.**—Four of the 10 eligible data sets reported pGLSRa.<sup>17-20,22</sup> Of these four, three used the full RV myocardium method,<sup>17-20</sup> and one data set used the RVFW-only method.<sup>22</sup> Normal mean values of pGLSRa for all four data sets combined varied from  $1.00$  to  $1.30$  sec<sup>-1</sup> (mean,  $1.18$  sec<sup>-1</sup>; 95% CI,  $1.04$ – $1.33$  sec<sup>-1</sup>). Between-study heterogeneity was not evidenced by a Cochran's Q statistic of 4.13 ( $P = .248$ ) and inconsistency by an  $I^2$  value of 27.3%. Because only one data set used the RVFW-only method, this may explain the difference in heterogeneity findings between pGLSRa 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, middle, and basal ventricular levels of the RVFW and has been clinically used to assess RV function in both adult and pediatric disease.<sup>23,24,31</sup> Five of the 10 eligible data sets in this meta-analysis reported segmental RV strain at all three levels of the RVFW.<sup>13,16,18-20,23,24</sup> Of these, three used the full RV myocardium method,<sup>16,18-20</sup> and two data sets used the RVFW-only method<sup>13,23,24</sup> to generate RV segmental longitudinal strain. The meta-analysis demonstrated a significant ( $P < .05$ ) base-to-apex gradient for the mean values of normal RV segmental strain ( $-33.53\%$ ,  $-32.33\%$ , and  $-29.16\%$ , respectively; Figure 5). Between-study heterogeneity was evidenced by a Cochran's Q statistic ranging from 32.81 to 51.74 ( $P < .001$ ) and inconsistency by an  $I^2$  value ranging from 87.8% to 94.5%. The heterogeneity for the segmental strain at the basal and middle ventricular levels of the myocardium was not explained by the different methods or by age, gender, BSA, HR, tissue-tracking methodology, frame rate, or

**Table 2** Echocardiographic characteristics

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

EP, EchoPAC; 4CH, four-chamber; NS, not specified.

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

\*Van der Hulst *et al.* produced two studies<sup>23,24</sup> that used the same control population; the author recommended using the 2010 study in the analysis.<sup>23</sup> The results were the same, but the 2010 study used 19 controls and the 2011 study used 18.

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

‡Cua *et al.* is a combination of two studies by Moiduddin *et al.* (2010)<sup>19</sup> Ozcelik *et al.* (2012)<sup>20</sup>; the last author provided a data set that combined both studies ( $n = 13$  control patients).

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 ( $P = .662$ ).

### Publication Bias

Both visual inspection of the funnel plot and the nonsignificant results of Egger's test for the global longitudinal strain measures ( $P = .59$ ) suggested the absence of publication bias (Figure 6).<sup>26,27</sup> Peak global longitudinal strain was identified in all 10 eligible studies for this meta-analysis.<sup>26,27</sup>

### Sources of Variability

In this meta-analysis, age, gender, BSA, HR, 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.*'s<sup>25</sup> study of normal left ventricular strain values, but our study also independently assessed equipment, software, probe size, and the number of cardiac cycles stored during acquisition. The software tracks myocardial motion through the cardiac cycle, calculating myocardial deformation from echogenic speckles in the B-mode image.<sup>12</sup> 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.<sup>12</sup> We also stratified the meta-analysis by the method of generating the strain measurements: RVFW only versus 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.

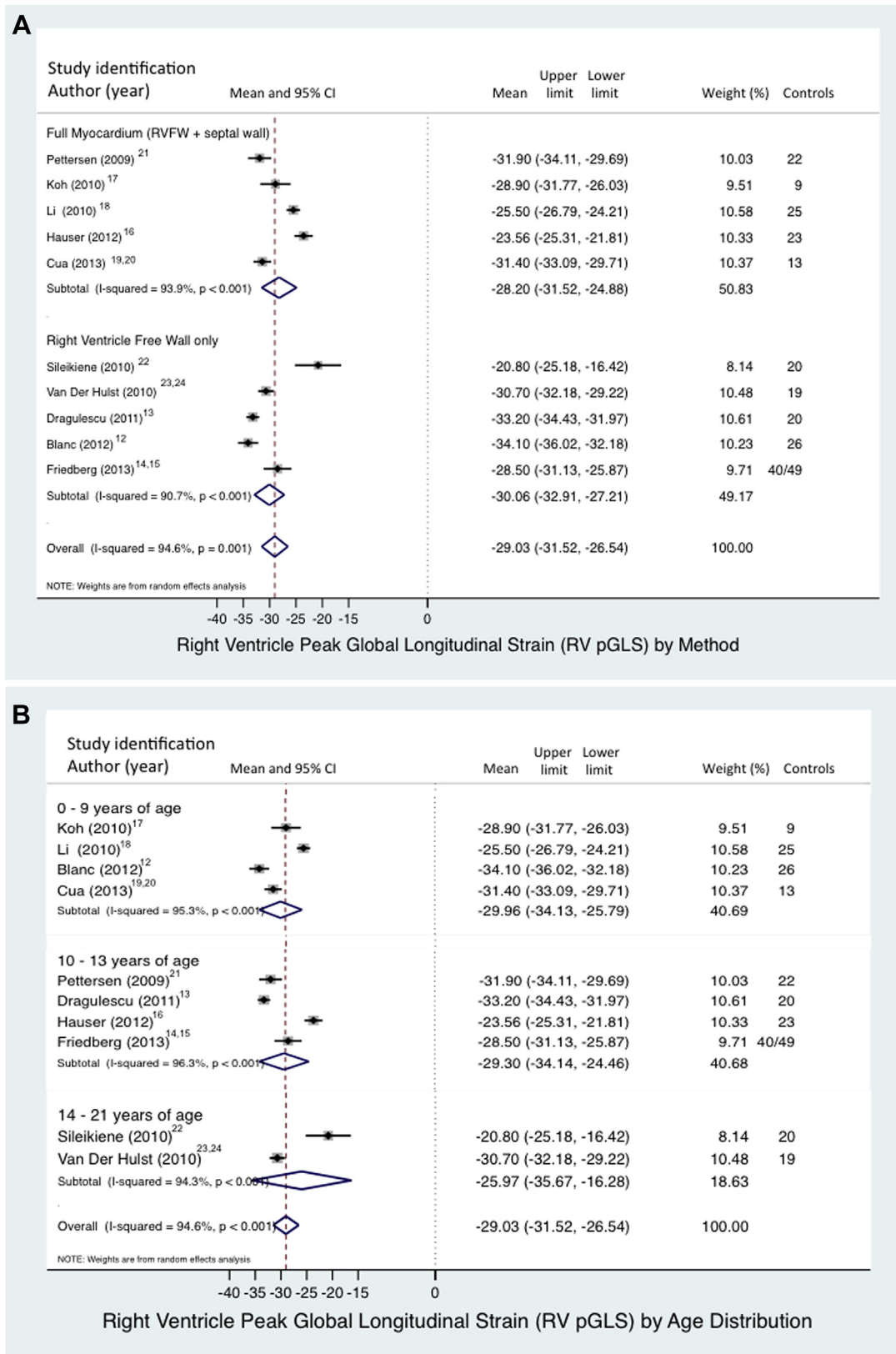
To thoroughly examine which parameter might statistically influence the variation in strain measures in this meta-analysis, we performed individual metaregression analysis on each dependent strain measure and each independent variable. None of the demographic, clinical, or echocardiographic variables were significantly

associated with the mean values for any of the seven strain measures (Table 3). We could not assess if blood pressure or intervender equipment or software was independently associated with the reported variations. Blood pressure was not reported in all of the eligible studies, and each study used a specific 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.

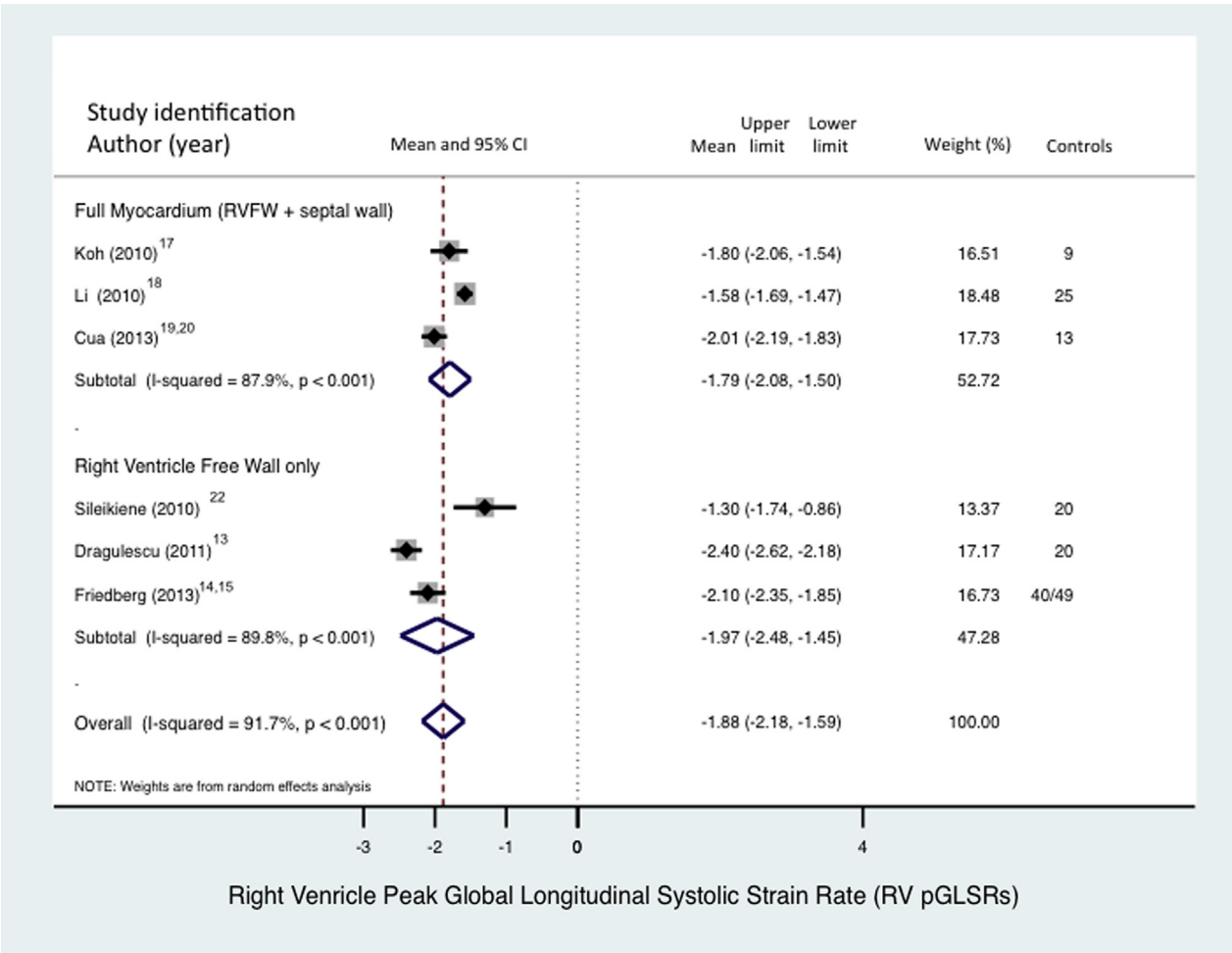
### DISCUSSION

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 arteriosus, and congenital and acquired heart disease.<sup>12-25,32-34</sup> 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.<sup>11</sup> 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 we are aware of to use systematic review and meta-analysis to define normal values of strain. Yingchoncharoen *et al.*'s<sup>25</sup> 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.<sup>25</sup> In this study, we evaluated RV global and regional systolic and diastolic deformation parameters in children. We added to this meta-analysis process by (1) increasing the number of search engines from three to five and searching [ClinicalTrials.gov](http://ClinicalTrials.gov) to check for



**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 chronologic order and the means and CIs 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% CI. The overall meta-analysis measure of effect is plotted as a diamond with the lateral points of the diamond indicating CIs for this mean estimate.



**Figure 4** Normal values of RV pGLSRs. The forest plot lists the names of the included studies in chronologic order and the means and CIs 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% CI. The overall meta-analysis measure of effect is plotted as a diamond with the lateral points of the diamond indicating CIs for this mean estimate.

ongoing studies related to our topic; (2) using a trained librarian to create search hedges to cover “concepts” (pediatrics and children, speckle-tracking, and the right heart ventricle) 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 e-mail to fill in gaps in the data in an attempt to decrease heterogeneity among studies and to publically notify them of the meta-analysis; and (4) independently (by two authors) selecting and reviewing all the eligible studies, and assessing their quality of publication.<sup>26-30</sup> Thus, combining our techniques with those of 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.

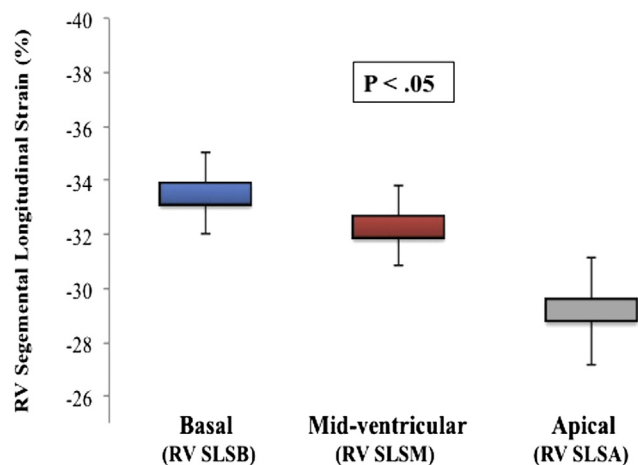
**Normal Ranges of Global Longitudinal Strain Measures**

This study defines normal values for RV global longitudinal strain (pGLS) and global longitudinal systolic (pGLSRs) and early and late diastolic (pGLSRe and pGLSRa) strain rate. All 10 eligible data sets

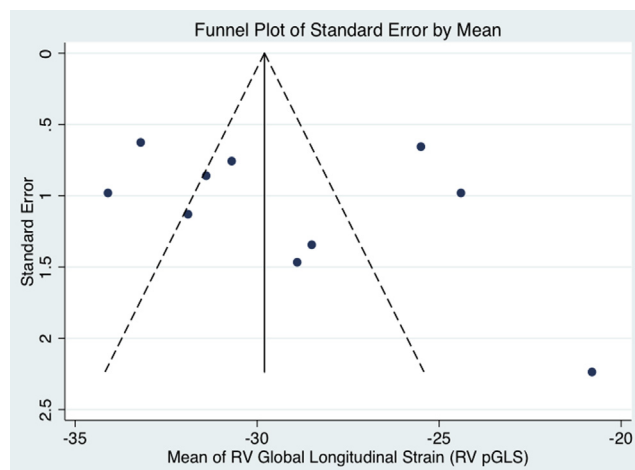
from 13 studies reported normal values of strain measures from small cohorts of healthy children. Except for the Munich Triathlon Heart Study,<sup>16</sup> which recruited healthy athletes, the other studies recruited healthy children to use as a control population to compare their myocardial deformation parameters with a diseased population in case-control observational study format.<sup>12-15,17-24,25</sup> 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.”<sup>25-30</sup>

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 two different methods, full RV myocardium and 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 to -1.6 sec<sup>-1</sup>; pGLSRe, 2.0 to 2.7 sec<sup>-1</sup>; pGLSRa, 1.0 to 1.3 sec<sup>-1</sup>). The different methods of generating strain measurements did not explain the heterogeneity in the reporting of different values among the studies. Left ventricular global longitudinal strain in healthy children has been reported as lower than RV global longitudinal strain.<sup>34-37</sup> In this study,





**Figure 5** Normal values of RV segmental longitudinal strain: (a) apical (RV SLA), (b) midventricular (RV SLSM), and (c) basal (RV SLSB). A significant base-to-apex gradient exists for RV segmental longitudinal strain ( $P < .05$ ).



**Figure 6** Publication bias. Funnel plot for studies of RV pGLS. The standard error of the effect estimate is plotted on the vertical axis. The mean of 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 ( $P = .59$ , Egger's test for statistical funnel plot symmetry).

RVFW-only values of pGLS may be higher than full RV myocardium ( $-30.06\%$  vs  $-28.20\%$ ) pGLS values because of 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, because 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 4.

### Normal Ranges of Segmental Longitudinal Strain Measures

The meta-analysis also defines normal ranges for segmental longitudinal strain at the apical, middle, and basal ventricular levels of the RVFW. Previous individual studies have demonstrated a base-to-apex segmental longitudinal strain gradient for the right ventricle in

children and adults,<sup>13,18-20,23,24</sup> 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 relatively constant geometry of the normal heart with maturation. The dominant deep longitudinal layers of the right ventricle are aligned base to apex and allow greater longitudinal shortening.<sup>38-40</sup> Alteration of this normal physiologic 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. The normal values for segmental longitudinal strain measures and their associated ranges are listed in Table 5.

### Clinical Impact of Normal Strain Values

With knowledge of the range of normal values of RV strain, we feel strongly that these myocardial deformation parameters can now be properly used to assess RV function in pathologic conditions in children. Two-dimensional STE-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.<sup>12-24</sup> Hauser *et al.*<sup>16</sup> also demonstrated the use of strain imaging to assess and track ventricular function in healthy children before and after endurance stress. Noninvasive strain imaging of the left ventricle is used to monitor the 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<sup>41</sup> and in children with primary RV failure or RV failure secondary to left heart conditions to prognosticate outcomes.

The recommended methods to quantitatively assess RV function in children include tricuspid annular plane systolic excursion, fractional area change, and RV myocardial performance index.<sup>1,4,5</sup> In comparison, strain imaging is the only echocardiographic parameter that evaluates both RV systolic and diastolic function at the global and segmental levels of the myocardial tissue at the same time.<sup>11,42,43</sup> The seven global and segmental strain measures analyzed in this meta-analysis have not all been consistently used and reported in clinical practice, but 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 metaregression in our study showed that the effects of age, gender, HR, BSA, frame rate, and probe size were not significant determinants of variations among normal ranges of reported strain measurements in children. Yingchoncharoen *et al.*<sup>25</sup> 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. Yingchoncharoen *et al.* also observed that changes in systolic blood pressure were independently associated with differences in the reported normal values of strain. Mean blood pressure was not documented or described in all 10 eligible studies, precluding its inclusion in the metaregression or assessment as a cause of heterogeneity. However, future studies that use strain as a measure of cardiac function in children should document blood pressure during the acquisition of the echocardiogram.<sup>25</sup>

**Table 3** Meta-regression results (*P* values) for RV global and segmental strain

Variable	pGLSRs	pGLSR <sub>Re</sub>	pGLSR <sub>a</sub>	Apical SLS	Middle SLS	Basal SLS
Age	.93	.38	.19	.60	.60	.08
Male Ggender	.88	.73	.89	.19	.19	.42
HR	.16	NA	NA	.38	.38	.43
BSA	NA	NA	NA	NA	NA	NA
Frame rate	.61	.22	.22	.90	.89	.10
Ultrasound scanner*	.10	.61	.47	.43	.14	.19
Vendor software*	.14	.35	.39	.94	.94	.40
Probe size	.18	.11	.24	.46	.46	.26
Tissue tracking	.34	.65	.47	.76	.94	.52

NA, Not analyzed because there were not enough variables; SLS, segmental longitudinal strain.

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

**Table 4** Normal RV global and SLS mean values

Variable	Mean	Upper 95% limit	Lower 5% limit
Global longitudinal strain measures*			
pGLS (%)	−29.03%	−31.52%	−26.54%
pGLSRs (sec <sup>−1</sup> )	−1.88	−2.18	−1.59
pGLSR <sub>Re</sub> (sec <sup>−1</sup> )	2.34	2.00	2.67
pGLSR <sub>a</sub> (sec <sup>−1</sup> )	1.18	1.04	1.33
SLS measures			
Apical SLS (%)	−29.16%	−32.99%	−25.33%
Middle SLS (%)	−32.33%	−35.42%	−29.24%
Basal SLS (%)	−33.53%	−37.64%	−29.42%

\*These normal values represent the combined normal values from the two methods used to generate the “global” strain: full RV myocardium and RVFW only.

Age did not explain the between-study heterogeneity of the reported normal ranges of values for pGLS. Colan *et al.*<sup>44</sup> 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.” RV strain changes throughout maturation from infancy to adolescence.<sup>36–38</sup> To account for this in reporting normal ranges of values in children, the meta-analysis was stratified by the age distribution in children: prepuberty (0–9 years), puberty (10–13 years), and late adolescence (14–21 years). The between-study *I*<sup>2</sup> value remained the same. The normal mean values of pGLS from prepuberty and puberty stages varied from −24% to −34% (mean, −29%). By adolescence (14–21 years of age), the normal range of pGLS 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 2D STE-derived left ventricular pGLS from our group<sup>36</sup> showed a significant relationship between pGLS and age from 0 to 18 years of age that was confirmed by Zhang *et al.*<sup>45</sup> with three-dimensional STE-derived pGLS.

We also intended to discern the role of vendor-specific ultrasound machines and vendor-customized software as a potential confounder of the variation in reported normal values of strain in healthy children, but all of the eligible studies used equipment and software from one manufacturer (GE Healthcare). Yingchoncharoen *et al.*<sup>25</sup> found that

of 28 eligible data sets, only five used non-GE equipment, and the use of different vendors was not an explanation of between-study differences in the reported values. Recent studies have not demonstrated significant variation between global longitudinal strain measures when different cardiac ultrasound systems were used for imaging acquisition and analysis.<sup>46–50</sup> Negishi *et al.*<sup>47</sup> 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. There were no eligible studies in a control cohort of children that used non-GE ultrasound machines or non-GE software to generate RV strain measures. The eligible studies in this meta-analysis used different GE models (Vivid E7, E9, and I) and different version of GE's 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 among the studies and were not significant variables in the metaregression (Tables 3 and 5). 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.<sup>25</sup> In comparison, there were fewer studies in children that used strain imaging to assess RV function. The sample size of 226 patients may be adequate to detect differences only 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 controlled studies.<sup>29</sup> All of the eligible studies in this meta-analysis were case-control or observational studies. Heterogeneity is an expected 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.<sup>26–30</sup> However, Yingchoncharoen *et al.*<sup>25</sup> also demonstrated high heterogeneity, and our study could not identify potential sources.

STE is a semiautomated software analysis program that is computer based but not user independent: the observer must initially place and then modify tracking region of interests.<sup>51,52</sup> There is a learning curve that is essential before introducing the technique into

**Table 5** Meta-regression results for pGLS

Variable	b (95% CI)	P
Age	0.17 (−0.68 to 1.01)	.66
Male gender	−0.33 (−1.29 to 0.63)	.44
HR	−0.36 (−0.78 to 0.06)	.21
BSA	−1.21 (−12.78 to 10.36)	.76
Frame rate	−0.11 (−0.33 to 0.11)	.27
Ultrasound scanner	−3.44 (−10.25 to 3.37)	.28
Vendor software	0.76 (−0.91 to 2.42)	.33
Probe size	−3.21 (−7.50 to 1.08)	.11
Tissue tracking	0.56 (−0.71 to 1.42)	.53

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, six of 10 data sets individually performed reproducibility analysis with the strain measurements (Appendix 3; available at [www.onlinejase.com](http://www.onlinejase.com)).

RV global longitudinal strain values are derived only from a single view, making it not a truly global assessment of RV function.<sup>42</sup> This meta-analysis pooled two methods that have been used 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 used 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 RV function in children in clinical practice.<sup>32,33,53,54</sup>

Peak global longitudinal strain 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. Postsystolic strain is defined as the total amount of deformation after valve closure.<sup>42</sup> Left ventricular postsystolic strain has been postulated as a marker of left ventricular ischemia, and RV postsystolic strain may reflect pathology in the systemic right ventricles.<sup>42</sup> Further studies are needed to interpret RV postsystolic values in children.

## CONCLUSIONS

In normal healthy children, the mean pGLS value is −29.03% (95% CI, −31.52% to −26.54%), mean pGLSRs is −1.88 sec<sup>−1</sup> (95% CI, −2.18 to −1.59 sec<sup>−1</sup>), mean pGLSRe is 2.34 sec<sup>−1</sup> (95% CI, 2.00 to 2.67 sec<sup>−1</sup>), and mean pGLSRa is 1.18 sec<sup>−1</sup> (95% CI, 1.04 to 1.33 sec<sup>−1</sup>). A significant base-to-apex gradient of pGLS in healthy children was observed from the meta-analysis. Variations among different normal ranges did 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 (GE Healthcare).

## SUPPLEMENTARY DATA

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.echo.2014.01.015>.

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## Appendix 1. Electronic Database 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): May 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): May 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): May 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 Central Register of Controlled Trials (Two Results): May 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 (Three Results): May 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 acquiring the images to the patient outcomes?

Was reproducibility analysis performed?

**Internal validity: confounding (selection bias)**

Were the cases and controls recruited over the same period of time?

Source: Downs and Black.<sup>28</sup>

### Appendix 3 Qualitative data for eligible data sets

Study	Year	Objective defined?	Outcome described?	Characteristics described?	Confounders described?	Main findings outlined?	Heterogeneous population?	Strain imaging protocol	Individuals generating data blinded to outcomes?	Sonographers blinded to outcome?	Was reproducibility analysis performed? <sup>§</sup>	Case/controls recruited over same time period?
Pettersen <i>et al.</i> <sup>21</sup>	2009	Yes	Yes	Yes	Yes	Yes	NS	Yes	No	No	Yes	NS
Koh <i>et al.</i> <sup>17</sup>	2010	Yes	Yes	Yes	Yes	Yes	NS	Yes	No	No	No	NS
Li <i>et al.</i> <sup>18</sup>	2010	Yes	Yes	Yes	Yes	Yes	NS	Yes	Yes	No	Yes	Yes
Sileikiene <i>et al.</i> <sup>22</sup>	2010	Yes	Yes	Yes	Yes	Yes	NS	Yes	No	No	No	NS
Van der Hulst <i>et al.</i> <sup>23,24,*</sup>	2010	Yes	Yes	Yes	Yes	Yes	NS	Yes	No	No	No	Yes
Dragulescu <i>et al.</i> <sup>13</sup>	2011	Yes	Yes	Yes	Yes	Yes	NS	Yes	No	No	Yes	NS
Blanc <i>et al.</i> <sup>12</sup>	2012	Yes	Yes	Yes	Yes	Yes	NS	Yes	Yes	No	Yes	NS
Friedberg <i>et al.</i> <sup>14,15,†</sup>	2013	Yes	Yes	Yes	Yes	Yes	NS	Yes	No	No	Yes	Yes
Hauser <i>et al.</i> <sup>16</sup>	2012	Yes	Yes	Yes	Yes	Yes	NS	Yes	NA	NA	No	No
Cua <i>et al.</i> <sup>19,20,‡</sup>	2013	Yes	Yes	Yes	Yes	Yes	NS	Yes	Yes	No	Yes	No

NS, Not specified.

\*Van der Hulst *et al.* produced two studies<sup>23,24</sup> that used the same control population; the author recommended using the 2010 study in the analysis.<sup>23</sup> The results were the same, but the 2010 study used 19 controls and the 2011 study used 18.

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

‡Cua *et al.* is a combination of two studies by Moiduddin *et al.* (2010)<sup>19</sup> Ozcelik *et al.* (2012)<sup>20</sup>; the last author provided a data set that combined both studies ( $n = 13$  control patients).

§Each of the studies that performed intraobserver and interobserver reproducibility analyses used a combination of Bland-Altman analysis, coefficients of variation, and/or intraclass correlation coefficient. In each study, it was reported that there were acceptably narrow limits of agreements, a coefficient of variation < 15%, and/or an intraclass correlation coefficient > 0.9.

Source: Downs and Black.<sup>28</sup>