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Publication Date

2023-11-01

DOI

10.1016/j.jelectrocard.2023.08.012

Peer reviewed

HHS Public Access

Author manuscript

J Electrocardiol. Author manuscript; available in PMC 2024 November 01.

Published in final edited form as:

J Electrocardiol. 2023 ; 81: 101–105. doi:10.1016/j.jelectrocard.2023.08.012.

Right and Left Ventricular Mass Development in Early Infancy: Correlation of Electrocardiographic Changes with Echocardiographic Measurements

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Abstract

Background: Right ventricular mass indexed to body surface area (RVMI) decreases and left ventricular mass index (LVMI) increases rapidly and substantially during early infancy. The relationship between these sizeable mass transformations and simultaneous electrocardiographic changes have not been previously delineated.

Methods: Normal term infants (#45 initially enrolled) were prospectively evaluated at 2 days and at 2-week, 2-month, and 4-month clinic visits. Ventricular masses were estimated with 2D echocardiographic methods. QRS voltages were measured in leads V_1, V_6, I and aVF.

Results: Mean QRS axis shifted from 135 (95%CI 124, 146) to 65 degrees (95%CI 49, 81) and correlated with both RVMI decrease and LVMI increase (R = 0.46* vs. 0.25† respectively. *p < 0.01, †p < 0.05). As RVMI decreased from mean 28.1 (95%CI 27.1, 29.1) to 23.3 g/m2 (95%CI 21.4, 25.2) so did V_1R and V_6S voltages. RVMI changes correlated with V_1R, V_6S, and V_1R+V_6S voltages (R = 0.29*, 0.23† and 0.35*, respectively. *p < 0.01, †p < 0.05) but not with V_1R/S ratio. As LVMI increased from 44.6 (95%CI 42.9, 46.3) to 55.4 g/m2 (95%CI 52.3, 58.5) V_6R and V_6Q increased but V_1S voltage did not. LVMI changes correlated with V_6R, V_6R-S, and V_6(Q+R)-S voltages (R = 0.31*, 0.34*, and 0.38* respectively. *p < 0.01) but not with V_1S or V_6R/S (R = 0.01 and 0.18 respectively, p = NS).

Conclusions: During early infancy the RVMI decrease correlates best with the QRS axis shift and V_1R+V_6S voltage, and the LVMI increase correlates best with V_6R-S and V_6(Q+R)-S voltages.

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Keywords

infancy; ventricular mass; electrocardiogram; echocardiogram

Introduction

Throughout fetal growth the left ventricle (LV) is consistently heavier than the right ventricle (RV) by direct measurement, but the RV/LV weight ratio is much higher than in postnatal life.[1] After 28 weeks gestation the RV rate of growth increases faster than the LV rate and the RV/LV ratio increases to a peak at birth.[1] Subsequently, following birth the heart undergoes a rapid transition to accommodate the hemodynamic changes of extrauterine life when the work of the LV increases and that of the RV decreases. In term infants the RV fraction of the total ventricular weight by direct measurement decreases from 44% at birth to 28% by 4 months.[2] During this time, using 2-D echocardiographic estimates, the RV mass indexed to body surface area (RVMI) decreases by 17% and the LV mass index (LVMI) increases by 24%.[3] Additionally, the RV:LV mass ratio decreases by 33% from 0.64 to 0.43. Thereafter, over the remainder of growth and maturity to adulthood, a much more gradual and smaller change occurs in indexed right and left ventricular mass with an additional average 21% decrease in the RV:LV mass ratio to 0.33 in males and 0.35 in females as estimated by magnetic resonance imaging.[4] The evolution in electrocardiogram (ECG) tracings during this rapid transition in early infancy has been detailed previously.[5–7] However, the correlations between these ECG changes and the simultaneous extensive ventricular mass variations have not been defined.

In a preceding study[3] the authors established the normal evolution of right and left ventricular mass during early infancy in normal term infants using two-dimensional echocardiographic methods that have been validated by comparison with magnetic resonance imaging.[8–9] Subjects in that study had 12-lead ECGs performed at the same time as the echocardiograms to screen for any congenital abnormality that would disqualify them from the study. However, the details of these tracings have not been previously analyzed or correlated to the ventricular mass changes. This study details the QRS voltage and axis measurements of these ECGs and compares them to the simultaneous changes in right and left ventricular mass as estimated by echocardiography.

Material and methods

The study population constituted healthy full-term appropriate for gestational age newborn infants from the nursery at Harbor-UCLA Medical Center who met criteria detailed in the previous publication.[3] Human subject research approval was obtained in advance from the Institutional Review Board of the Harbor–UCLA Research and Education Institute (now The Lundquist Institute). The subjects' parents gave informed written consent prior to enrollment. Procedures were followed in accordance with institutional guidelines and sedative medications were not used. Study participants were evaluated at 2 days of age in the nursery and at the time of their routine 2-week, 2-month, and 4-month well-baby pediatric clinic visits. Each evaluation included a detailed medical history, vital signs

(heart rate, respiratory rate, blood pressure and pulse oximetry), measurement of body length and weight, complete physical examination, standard scalar ECG, and a complete echocardiogram. Any significant abnormality led to exclusion from the study.

Twelve-lead ECGs were recorded at rest in the supine position using a MAC PC resting ECG analysis system (Marquette Medical Systems, Inc., Milwaukee, WI) with digital sampling rate of 2000 Hz at 10 mm/mV calibration and speed of 25 mm/s in the unfiltered mode. The previously well-defined standard protocol for electrode placement was used and extra care was given to using anatomical landmarks to ensure proper lead placement.[10] Measurements were made of the QRS voltages of limb leads I and aVF in the frontal plane and of precordial leads V_1) and V_6 in the transverse plane. Voltages were measured carefully using calipers to a precision of 0.25 mm in distance on the ECG tracing, which is 0.025 mV. When there was variability in QRS voltages within a lead tracing, the largest one was used for measurement. Leads I and aVF were used to calculate the mean QRS axis with the method recommended by Spodik et al.[11] Leads V_1 and V_6 were chosen for analysis since they are used in the pediatric criteria for left and right ventricular hypertrophy in the American Heart Association/American College of Cardiology/Heart Rhythm Society recommendations for the standardization and interpretation of the ECG and in the guidelines for the interpretation of the neonatal electrocardiogram by the European Society of Cardiology.[12–13] In addition to these standard criteria, the R/S voltage ratios and net RS voltages (R − S) were calculated in leads V_1 and V_6. Finally, the Q wave voltage in V_6, when present, was also measured, since it is reflective of ventricular septal depolarization and the septum is part of the LV. Then it was used to compute the V_6 net QRS voltage as (Q + R) - S. Intra- and interobserver variability were estimated with paired measurements on 10 sets of different subject ECG tracings. Variabilities were measured by Pearson correlation coefficients and mean differences expressed as absolute mV and percentage.

Echocardiograms were obtained using an Acuson 128XP-10 model echocardiographic instrument (Mountain View, CA) with 7 or 5 mHz probes. All echocardiographic measurements were made at end-diastole, over 4 consecutive cardiac cycles, to account for respiratory variation. Mean values for all measurements were used in subsequent calculations. Maximal ventricular cavity size was used to define end-diastole. LV mass was estimated with the area–length method.[9] RV free-wall mass was estimated with the one-quarter prolate ellipsoid shell formula: RV free-wall mass = 5.84 (RV cavity area) (RV free-wall thickness) + 1.0, where RV cavity area was measured in the apical 4-chamber view and RV free-wall thickness was obtained in the subcostal coronal or sagittal view.[8] To account for growth and body size, the ventricular measurements were indexed to body surface area (BSA). In this study BSA was calculated from height and weight according to the formula of Mosteller,[14] since a recent evaluation of six BSA formulas in infants and young children demonstrated that it was the best one to use in infancy.[15] The older DuBois formula, which we previously used, was found to underestimate and the widely used Haycock formula to overestimate the BSA in this age group. RV and LV mass were also expressed as fractions of the total ventricular mass. The ECGs and echocardiograms were reviewed by two authors at each period to ensure completeness and normality. Measurements made by JJJ were used in the analysis. Correlation coefficients between ECG and echocardiographic parameters

were calculated with Pearson's linear regression analysis. P value < 0.05 was considered statistically significant. Results are presented as mean with standard deviation or 95% confidence intervals. Analyses were performed using SPSS Statistics for Windows, Version 26.0, IBM Corp., Armonk, NY.

Results

Forty-five (15 males and 30 females) of 50 infants that were initially evaluated met criteria and were enrolled at age 2 days. Gestational age at birth was 39 ± 1 week. Due to the availability of neighborhood clinics for subsequent well-infant care, the number of subjects returning for follow-up decreased throughout the study period. Patient demographics and clinical characteristics including age, length, weight, resting heart rate, mean blood pressure, and ventricular measurement data are listed in our original article **(See** Supplemental Tables 1 **to** 3).[3] Using the more appropriate Mosteller formula[14] for infant BSA calculation in this re-evaluation, the RVMI and LVMI values are listed in Table 1 along with the simultaneous ECG values. As the RVMI decreased with growth, so did the voltage of the R wave in V_1 and the voltage of the S wave in V_6. As the LVMI increased, the R wave voltage in V_6 increased but the S wave voltage in V_1 did not. The percentage of patients with q waves present in lead V_6 increased with growth and the concomitant increase in LVMI from 60% at 2 days to 63% at 2-week and 80% at 2- and 4-week follow-up evaluations. The decrease in RVMI and increase in LVMI were reflected in a concomitant shift in the mean QRS axis. The linear correlation coefficients of the various ECG measurements with the changes in the RVMI, RV mass fraction, LVMI, and LV mass fraction are presented in Table 2. The standard ECG criterion that had the highest correlation with RVMI is displayed in Figure 1. A new proposed ECG criterion, (Q + R) - S voltage in V_6, which had the best correlation with LVMI and LV mass fraction, is exhibited in Figure 2. Mean intra-observer variability of QRS measurements were from 0.002 to 0.022mV or 1 to 12% with correlation coefficients of 0.99. Mean interobserver variability of QRS measurements were from 0.004 to 0.023mV or 1 to 18% with correlation coefficients of 0.94 to 0.99.

Discussion

In this study we used contemporaneous ECG and echocardiography to correlate the respective extensive developmental changes in each from just after the brief transitional period of the first day following birth through the initial third of infancy. A standard 12-lead ECG with carefully placed leads was followed by an echocardiogram at the same time. Two-dimensional echocardiographic methods validated by comparison with magnetic resonance imaging were used for the estimation of RV mass and LV mass.[8–9] We showed a mean QRS axis shift of 70 degrees from rightward to leftward in the frontal plane and the mean voltage in lead I increased by 0.67 mV from an average −0.39 mV initially to +0.28 mV at four months. This is in keeping with other studies that have demonstrated a dramatic counterclockwise change in the QRS axis in the frontal plane and a change in polarity in lead I net voltage as a result of rapidly increasing LV dominance through the first several months after birth.[5,16]

Our study showed that the leftward shift in the mean QRS axis was correlated both to the decrease in RVMI and the increase in LVMI. The decrease in RVMI also correlated significantly with the sum of $V_1R + V_6S$ voltages and less so with each individually. The LVMI increase correlated with V_6R voltage but less with the sum of $V_6R + V_1S$ voltages since there was no correlation to V_1S voltage. The initial decrease in V_1S voltage during early infancy has been documented in previous ECG studies.[5–7] Furthermore, prior ECG studies in children and adolescents by Ramaswamy et al[17] and adolescent athletes by Czosek et al[18] also did not show a significant correlation between LVMI and V_1S voltage. A more recent and much larger study of all pediatric ages from infancy to 18 years old by Tague et al[19] found only a very weak correlation between LVMI and V_1S voltage over that large age range with $R = 0.14$. The correlation of V_6R to LVMI was significant in the studies by Ramaswamy et al[17] and Tague et al[19] with $R = 0.31$ and $R = 0.24$, respectively. In addition to evaluating the R wave voltage alone in V_6 as indicative of LV forces, we compared the net voltage(s) attributable to the LV minus the voltage attributable to the RV with the LVMI and LV mass fraction. V_6R-S and V_6(Q+R)-S were noted to have stronger correlation coefficients to LV mass than V_6R alone.

The R/S voltage ratio in V_1 and surprisingly even that in V_6 did not correlate significantly to RVMI or LVMI in our study. Liebman[20] previously noted that the R/S ratio in V_1 was a poor criterion for RV hypertrophy and appeared to be mainly reflective of the proximity effect due to the heart being closer to the anterior electrodes in infants. Brockmeier[16] also described this proximity effect in infants and attributed it to a large heart to chest ratio, the anterior location of the heart within the chest cavity and the water content of intervening tissues (thymus) contributing to large voltage amplitudes in V_1.

The pediatric ECG criteria for diagnosis of ventricular hypertrophy recommended by the American Heart Association, the American College of Cardiology, and the Heart Rhythm Society,[12] along with the European Society of Cardiology[13] involve the voltages of V_6R voltage, V_1S voltage, and V_1S voltage + V_6R voltage combined for left ventricular hypertrophy and V_1R voltage, V_6S voltage, and V_1R voltage + V_6S voltage combined for right ventricular hypertrophy. The standards for these voltage thresholds were derived from a large population of clinically normal children reported by Davignon et al.[6] While ECG variations related to ethnicity/race or sex have been documented in children three years of age or older, this has not been noted in infancy.[7, 21] Thus, in our small study we did not stratify by sex or ethnicity/race. The lack of correlation between LVMI and V_1S voltage in our infant study and the above-mentioned studies in children and adolescents [17–19] should compel us to be hesitant to use voltage criteria in this lead alone to diagnose LV hypertrophy in pediatric patients. Similarly, the R/S voltage ratios in V_1 and V_6, which did not correlate with RVMI or LVMI in our study, are not likely to be useful criteria for diagnosing ventricular hypertrophy in infancy. The V_6(Q+R)-S voltage, uniquely described in this study, could be further investigated as an improved criterion for diagnosing LV hypertrophy in early infancy. Previous studies in children and adolescents have shown that the ECG is a generally poor screening test for diagnosing echocardiographic left ventricular hypertrophy due to a low sensitivity. [17–19] However, a similar ECG-echocardiogram study limited to early infancy, when congenital heart disease most commonly presents clinically, has not yet been done.

Lastly, it is noteworthy that our study in early infancy, when there is a dramatic shift in the masses of the RV and LV, showed an improved correlation between the ECG criteria and LV mass when expressed as a fraction of total ventricular mass rather than when indexed to body surface area. However, this difference was not evident for RV mass, which has a more anterior position in the chest. This implies that the RV mass has a significant effect on the V_6 voltages, while the LV mass has minimal effect on the V_1 voltages. Future studies could also investigate this relationship further.

The main limitation of our study was the relatively small number of subjects with incomplete retention. These results are only representative of term infants with normal weights. The strengths of the study were that it was prospective and extra care was taken to place the ECG electrodes in their precise locations and to carefully obtain the echocardiographic measurements required for estimation of ventricular mass.

Conclusions

In conclusion, during early infancy RVMI correlates best with the mean QRS axis and the sum of $V_1R + V_6S$ voltages and LVMI correlates best with V_6R-S voltage and $V_6(Q+R)$-S voltage. The lack of correlation by V_1S voltage and the V_6R/S voltage ratio with LVMI, and the similar lack of correlation by the V_1R/S voltage ratio with RVMI, should compel us to be hesitant to use these criteria for determination of ventricular hypertrophy in early infancy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This study was supported by the Perinatal Clinical Research Center, The Lundquist Institute at Harbor-UCLA Medical Center (previously the Research and Education Institute), Torrance, CA and grant MO1 RR 00425 from the National Institutes of Health, Bethesda, MD. We thank the nurses, especially Sylvia Villanueva, RN, and Christine Mori, RN, in the Perinatal Clinical Research Center and James L. Reynolds, MD, of Tulane University for their invaluable help.

James J. Joyce, MD and Research and Education Institute, Torrence, CA reports administrative support and equipment, drugs, or supplies were provided by National Institutes of Health. Ruey-Kang Chang, MD reports a relationship with QT Medical Inc. that includes: board membership and employment.

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Highlights

- In early infancy indexed right ventricular mass decreases while the left increases.
- Right ventricular mass index changes correlate best with the QRS axis shift.
- Left ventricular mass index changes correlate best with V_6 (Q+R)-S voltage.
- V_1R/S voltage ratio does not correlate with right ventricular mass index.
- V_1S voltage and V_6R/S voltage ratio do not correlate with left ventricular mass index.

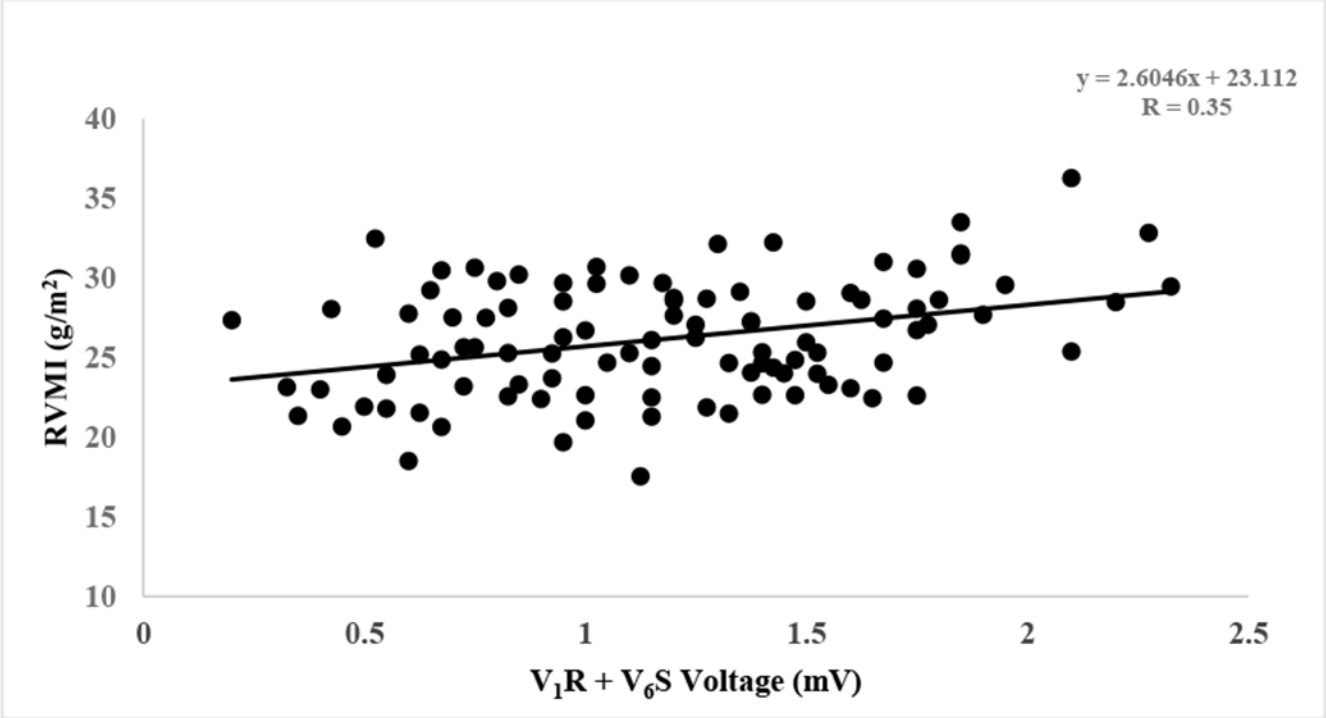

Figure 1.
$V_1R + V_6S$ Voltage (mV) vs. RVMI (g/m^2) ($p < 0.01$)

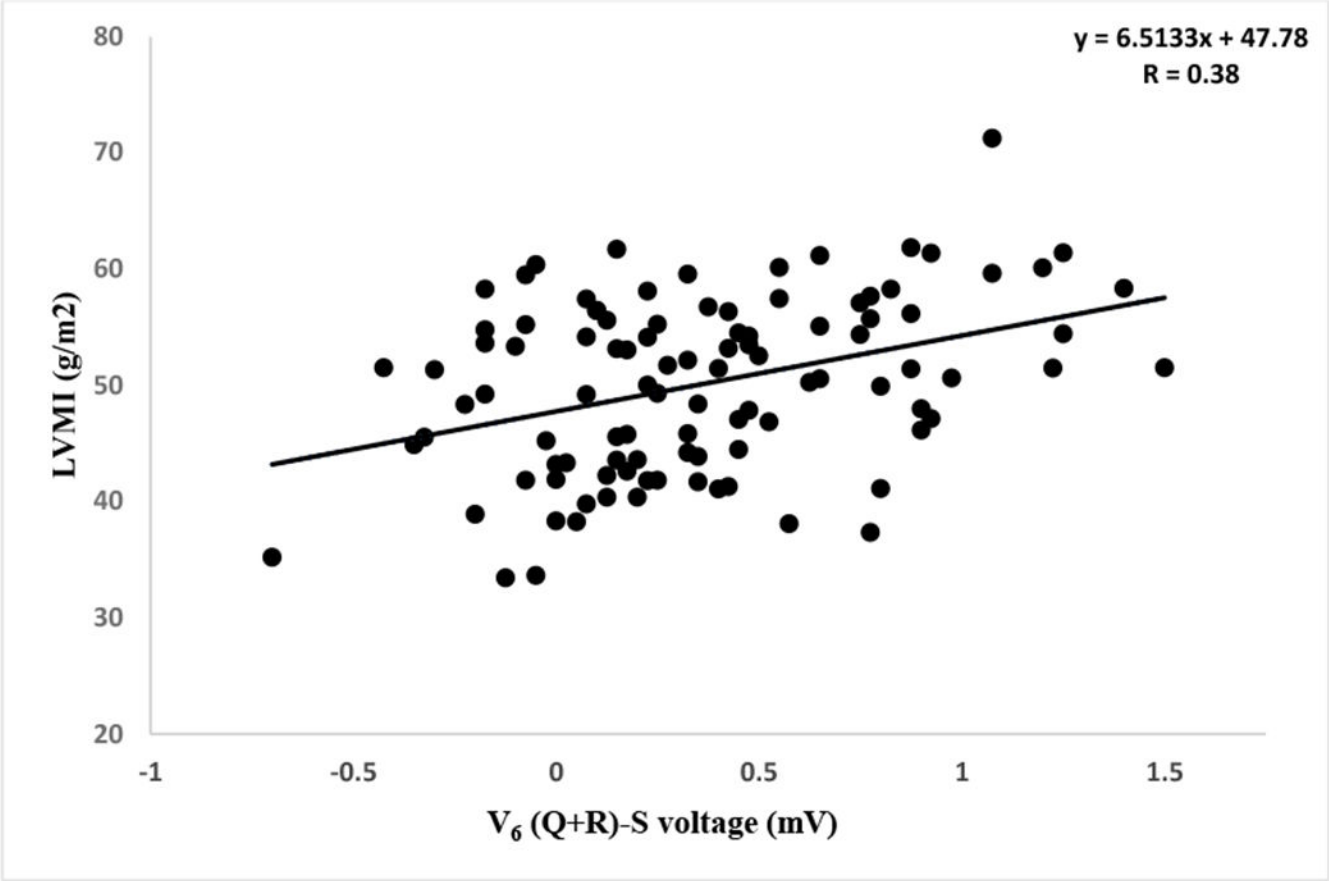

Figure 2.
V_6 (Q+R)-S Voltage vs. Left Ventricular Mass Index ($p < 0.01$)

Table 1.

Simultaneous Echocardiographic and Electrocardiographic Data at Different Ages

Parameter Subject number	2 Day 45	2 Week 27	2 Month 20	4 Month 15
BSA (m^2)	0.21	0.23	0.30	0.35
	(0.20, 0.22)	(0.22, 0.24)	(0.29, 0.31)	(0.33, 0.37)
RVMI (g/m^2)	28.1	26.0	24.8	23.3
	(27.1, 29.1)	(24.9, 27.1)	(23.7, 25.9)	(21.4, 25.2)
LVMI (g/m^2)	44.6	53.1	55.1	55.4
	(42.9, 46.3)	(51.0, 55.2)	(52.7, 57.5)	(52.3, 58.5)
QRS Axis (degrees)	135	134	74	65
	(124, 146)	(122, 146)	(60, 88)	(49, 81)
V_1 R voltage (mV)	1.20	0.88	0.72	0.73
	(1.10, 1.30)	(0.74, 1.02)	(0.58, 0.86)	(0.56, 0.90)
V_1 S voltage (mV)	−0.58	−0.35	−0.34	−0.37
	(−0.46, −0.70)	(−0.23, −0.47)	(−0.21, −0.47)	(−0.23, −0.51)
V_1 RS net voltage (mV)	0.62	0.54	0.37	0.36
	(0.48, 0.76)	(0.42, 0.66)	(0.25, 0.49)	(0.20, 0.52)
V_1 R/S ratio (mV)	3.8	5.1	3.5	2.7
	(2.6, 4.9)	(3.1, 7.1)	(2.4, 4.6)	(1.9, 3.5)
V_6 S voltage (mV)	−0.23	−0.24	−0.21	−0.18
	(−0.15, −0.31)	(−0.18, −0.30)	(−0.10, −0.32)	(−0.11, −0.25)
V_1 R + V^6 S voltage (mV)	1.43	1.12	0.93	0.90
	(1.30, 1.56)	(0.95, 1.29)	(0.74, 1.12)	(0.71. 1.09)
V_6 R voltage (mV)	0.34	0.37	0.83	0.84
	(0.27, 0.41)	(0.27, 0.47)	(0.66, 1.00)	(0.65, 1.03)
V_6 RS net voltage (mV)	0.06	0.10	0.55	0.58
	(−0.03, 0.15)	(0.01,0.19)	(0.44,0.66)	(0.39,0.77)
V_6 R/S ratio (mV)	3.5	2.5	5.1	8.3
	(1.5, 5.5)	(1.2, 3.8)	(3.9, 6.3)	(3.3, 13.3)
V_6 QRS net voltage (mV)	0.15	0.18	0.70	0.75
	(0.05, 0.24)	(0.08, 0.28)	(0.57, 0.83)	(0.52, 0.98)

Mean (95% confidence intervals)

Table 2.

Correlation Coefficients of Electrocardiographic Measures to Ventricular Mass

ECG Parameter	RVMI	RV mass fraction	LVMI	LV mass fraction
QRS Axis	0.46 *	0.40 *	0.25 †	0.40 *
V_1 R voltage	0.29 *	0.27 *	--	--
V_1 R-S voltage	0.19	0.21 †	--	--
V_1 R/S voltage ratio	0.15	0.13	--	--
V_6 S voltage	0.23 †	0.23 †	--	--
V_1 R + V_6 S voltage	0.35 *	0.33 *	--	--
V_1 S voltage	0.11	0.06	0.01	0.06
V_6 R voltage	--	--	0.31 *	0.40 *
V_6 R-S voltage	--	--	0.34 *	0.50 *
V_6 (Q+R)-S voltage			0.38 *	0.51 *
V_6 R/S voltage ratio	--	--	0.18	0.23 †
V_6 R + V_1 S voltage	--	--	0.23 †	0.25 †

* $p < 0.01$,

† $p < 0.05$