
ORIGINAL COMMUNICATIONS

ELECTROCARDIOGRAM ANALYSIS IN ADULT PATIENTS WITH SICKLE CELL DISEASE

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This study is an analysis of the electrocardiograms (ECGs) of 87 adult patients taken during hospital admission for sickle cell disease (homozygous S). The age range was 18 to 55 years: 38 were men and 49 were women. Seventy-two percent of all patients had abnormal ECGs. Non-specific ST-T (NS-ST-T) wave abnormalities (53 percent) and QT interval prolongation (12 percent) were frequent. Seventy-five percent of the normal ECGs occurred in women ($P < .05$); and 74 percent of those with left ventricular hypertrophy (LVH) were men ($P < .05$). Fifteen of 21 (71 percent) patients with arrhythmias had NS-ST-T abnormalities. Systemic hypertension and ECG evidence for right-sided heart disease were rare, as was the incidence of LVH by ECG.

One of the first large studies of the electrocardiogram (ECG) in patients with sickle cell disease (SCD) was published in the *East African Medical Journal* in 1962.¹ As in the other studies in the literature, the majority of the subjects were children.²⁻¹³ No large studies of adults have been reported previously. This study was undertaken to ascertain the incidence and

types of ECG abnormalities in a large sample of adult patients with homozygous hemoglobin S.

Sickle cell disease is an important medical problem with major economic and social implications in addition to multiple system organic problems. In addressing cardiac abnormalities, the lack of a reference database for adult patients has been emphasized.¹⁴ Documentation of the ECG findings in a large number of adult patients will provide the basis for confidence in the reliability of published findings for the group as a whole.

METHODS

The clinical records of 100 adult patients, aged 18 years or older, were randomly selected from a database of 756 patients admitted to the Los Angeles County/University of Southern California Medical Center with the diagnosis of homozygous sickle cell disease (HbSS). Eighty-seven patients met the requirement of documented HbSS and had at least one ECG taken during the reference admission while clinically stable. The age and sex distribution of patients is given in Table 1.

The diagnosis of SCD was confirmed by hemoglobin electrophoresis, and notations were made of all associated diagnoses, electrolyte disturbances, or therapy that might independently alter the ECG. The following clinical information and laboratory measurements were recorded: age, sex, associated illness, and hemoglobin, hematocrit, red blood cell count, total bilirubin, serum lactic acid dehydrogenase, and reticulocyte count levels, and the presence or absence

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TABLE 1. AGE AND SEX DISTRIBUTION IN ADULTS WITH SICKLE CELL DISEASE (n = 87)

Age Group	Total (No.)	Male (No.)	Female (No.)
18-19	7	4	3
20-29	56	24	32
30-39	16	7	9
40-49	7	3	4
50-59	1	0	1
Mean age	27	27	28
Total	87	38	49

of current or previous clinical evidence for congestive heart failure with reference to specific cause.

Cardiac physical signs were recorded, including systolic and diastolic murmurs, ejection click, accentuated pulmonic component of the second heart sound, third heart sound and fourth heart sounds, and pulmonary rales. Most of the physical findings were recorded from senior physician or attending staff's notes. Chest roentgenogram findings were also recorded.

Electrocardiographic Procedure and Criteria

All electrocardiograms were taken in the supine position at rest using standard single-channel and three-channel machines, which met American Heart Association standards. All ECG measurement criteria were taken from prior studies with defined databases.

Criteria for left ventricular hypertrophy were as follows: (1) SV_1 plus R in V_5 or $V_6 \geq 35$ mm for patients aged 26 years or older, and ≥ 53 mm for those aged 18 to 25 years^{15,16}; and (2) voltage in lead AVL ≥ 13 mm.

For abnormal ST-T waves the following criteria were used: (1) ≥ 1 mm depression or elevation (convex) of the ST segment from baseline¹⁷; (2) notched, inordinately peaked, biphasic, flat or inverted T waves^{17,18}; and (3) a QRS-T angle of $\geq 60^\circ$.^{7,17}

QT interval prolongation was calculated as:

$$QT_c = \frac{QT_m}{R-R} > 44/\text{sec}$$

where QT_c = QT corrected for heart rate

QT_m = measured

R-R = cycle interval¹⁹⁻²³

Left atrial enlargement was diagnosed if the product of the duration and magnitude of the negative terminal force of the P wave in lead V_1 was ≥ 0.03 mm sec.²⁴

Left anterior hemiblock was defined as: (1) left axis deviation (-30° to -90° QRS axis); (2) a small Q wave in lead I and AVL; and (3) a QRS of < 0.12 sec, if this was an isolated defect.²⁵

Right bundle branch block was defined as a ≥ 0.12 sec QRS with terminal right anterior forces.²⁶

In addition, measurements of parameters of the electrocardiogram were made in milliseconds in leads II and V_1 for the following: P-wave, P-R, QRS, and QT intervals as well as heart rate. Arrhythmias and specific ECG abnormalities were also recorded.

The records of patients who had electrolyte imbalances, or who were receiving cardioactive drugs, and of those who had known organic heart disease due to specific causes (eight and five patients, respectively) were removed from the group data analysis.

For comparison of group differences, the Pearson chi-square test was used, and for comparison of differences between means, the Student's *t* test, two-tailed with separate variance, was used.

RESULTS

All of the patients were adults (≥ 18 years). Seventy-two percent (63 of 87) were ≥ 30 years of age, while 44 (51 percent) were ≤ 25 years, and 43 (49 percent) were above 25 years of age (Table 1). The mean age of all patients was 27 years. Laboratory characteristics of the group are shown in Table 2 and clinical findings in Table 3.

Systolic murmurs occurred in 68 of 87 patients (78 percent) and were associated with lower hemoglobin values (8.15 vs 9.18 g/dL, $P < .01$), lower hematocrits (24 vs 28 vol%, $P < .01$), and lower red cell counts (2.62 vs $3.13 \times 10^6/\mu\text{L}$, $P < .04$). No other findings appeared consistently. Cardiomegaly was present on chest x-ray film in 66 percent of patients (57 of 87).

General ECG Abnormalities

Abnormal ECGs were present in 63 of 87 (72 percent) patients. Of the 24 patients with normal ECGs, 18 (75 percent) were women and 6 (25 percent) were men ($P < .05$) (Figure 1).

TABLE 2. ECG INTERVAL AND PATIENT LABORATORY RESULTS

ECG Interval and Laboratory Test	Mean	Minimum	Maximum
PR interval (sec)	.16	.11	.24
QR interval (sec)	.40	.32	.52
Heart rate (beats/min)	82	45	125
QRS duration (sec)	.08	.07	.12
Hemoglobin (g/dL)	8.2	3.9	11.9
Hematocrit (vol %)	25	12	38
Red blood cell count ($\times 10^6/\mu\text{L}$)	2.7	1.5	4.9
Total bilirubin (mg %)	3.9	0.6	37
Lactate dehydrogenase (U/L)	1,168	520	3,350
Reticulocyte count (% counted)	9	0.3	23

TABLE 3. PHYSICAL AND CHEST X-RAY EXAMINATION RESULTS OF PATIENTS WITH ORGANIC HEART DISEASE

	Patients No. (%)	No. of Men	No. of Women
Diastolic murmur	4 (5)	1	3
Ejection click	1 (1)	0	1
Accentuated P ₂	6 (7)	3	3
Systolic murmur	68 (78)	29	39
Third heart sound	5 (6)	2	3
Fourth heart sound	9 (10)	5	4
Pulmonary rales	3 (3)	0	3
Cardiac enlargement	57 (66)	23	34
Increased pulmonary artery size	11 (13)	4	7
Pulmonary venous redistribution	26 (30)	11	15

Repolarization abnormalities were frequent. Non-specific ST-T wave abnormalities (NS-ST-T) occurred in 43 of 87 (52 percent) and prolonged QT intervals in 9 of 87 (11 percent); these were often concurrent ($P < .005$) (Figure 2). Fifteen of 21 (71 percent) patients with other than normal sinus arrhythmia had NS-ST-T abnormalities, but these were not statistically associated with other ECG findings.

Left ventricular hypertrophy (LVH) occurred in

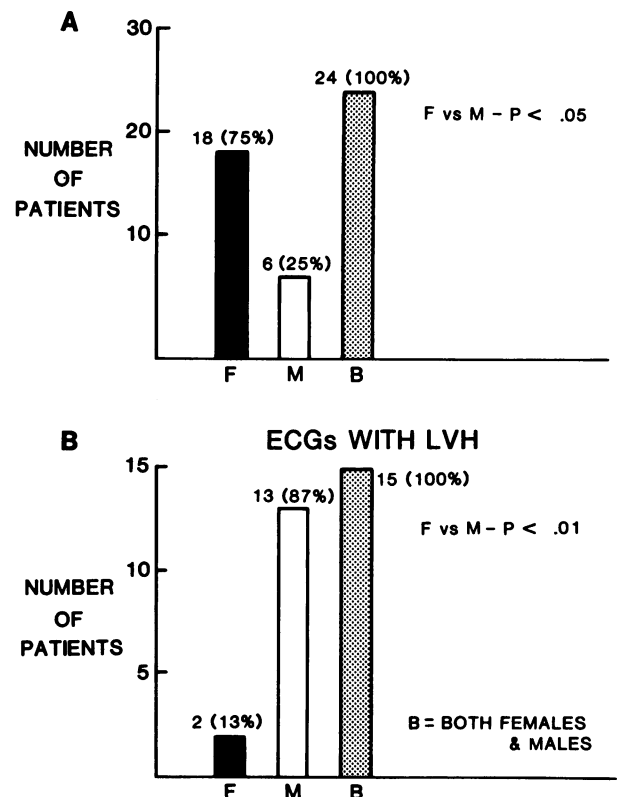


Figure 1. Graphs A and B show the distribution of male and female patients with normal ECGs and those with left ventricular hypertrophy. The clear predominance of women among the patients with normal ECGs and of men among those with abnormal ECGs is clearly evident

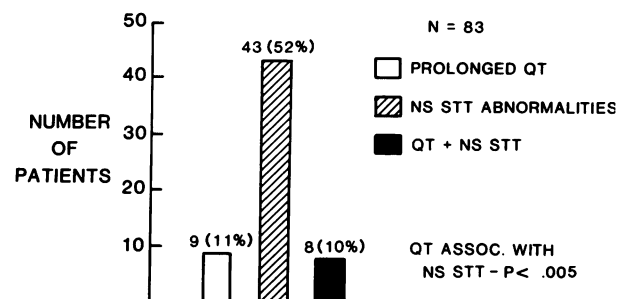


Figure 2. The distribution of repolarization abnormalities in the study sample. The combination of QT prolongation and nonspecific ST-T wave abnormalities occurred with a frequency that was statistically significant

15 (22 percent) patients and was more frequently seen in men (13) than in women (2), ($P < .01$) (Figure 1). Patients with LVH had slightly longer P-R intervals

compared with those without, mean 0.169 ± 0.006 and 0.156 ± 0.003 seconds, respectively ($P < .05$), and also had slower heart rates (77 vs 84 beats per minute, $P < .05$). The differences in mean LV voltage ($SV_1 + RV_5$ or V_6) between patients ≥ 25 years of age and younger patients were nonsignificant (36.67 ± 10 and 33.66 ± 10 mV). Only one patient ≤ 25 years of age met strict LVH criteria ($P < .05$). Men had measurably wider mean QRS intervals than female patients (0.09 vs 0.08 sec, $P < .01$). Interestingly, hemoglobin (Hgb) and hematocrit (Hct) values were also higher in men than in women (Hgb 8.8 vs 7.8 g/dL, Hct 26 vs 24 vol%, respectively, $P < .01$).

Ten of 87 patients (11 percent) had sinus tachycardia and eight of those 10 (80 percent) were women ($P < .05$). Patients with sinus tachycardia had higher hematocrits than those without (27 vs 24 vol%, $P < .05$). The ECG findings are summarized in Table 4.

DISCUSSION

The data in this study confirm certain findings from previous ECG studies, but our findings are at variance with what has been published previously with respect to the incidence of right-sided heart disease as reflected in the ECG in patients with SCD.^{3-8,10,11,27} In this study, findings such as right atrial enlargement, right ventricular enlargement, right axis deviation, right bundle branch block, etc, were infrequent or absent (Table 4). Previous invasive, echocardiographic, and pathological studies support these findings of a low incidence of cor pulmonale ECG equivalents in SCD.^{3,11-14,28,29} Such patients may have been excluded because of the requirement for clinical stability for study entry.

Some previous reports suggest that the cardiac status does not deteriorate with age in SCD.³ All but one of the study patients with LVH were older than 25 years, which suggests a possible age-related progression.

This study confirms that both QT interval prolongation and nonspecific ST-T wave abnormalities are frequent and often concurrent findings in adults with SCD.⁷ These findings raise a question of the significance of myocardial repolarization alterations in this disorder.³⁰⁻³² Additional questions are raised: Are the electrocardiographic repolarization abnormalities in-

TABLE 4. ECG DIAGNOSES AND RHYTHMS IN PATIENTS WITH SICKLE CELL DISEASE (n = 87)

	Patients No. (%)	Male	Female
Left atrial enlargement	9 (10)	6	3
Left ventricular hypertrophy	19 (22)	14	5
Left anterior hemiblock	1 (1)	1	0
J point (normal variant) ST elevation	11 (13)	5	6
Nonspecific ST-T wave abnormalities	46 (53)	17	29
Prolonged QT interval	10 (12)	5	5
Incomplete right bundle branch block	1 (1)	1	0
Right bundle branch block	2 (2)	1	1
Within normal limits	24 (28)	6	18
Previous myocardial infarction	1 (1)	0	1
Low voltage	1 (1)	1	0
Right axis deviation	1 (1)	0	1
T-wave inversion V_{1-3}	1 (1)	0	1
Normal sinus rhythm	65 (75)	29	36
First degree AV block	1 (1)	—	—
Low atrial pacemaker	2 (2)	—	—
Sinus bradycardia	4 (8)	—	—
Premature ventricular beats	1 (1)	—	—
Sinus tachycardia	10 (12)	2	8
Sinus arrhythmia	2 (2)	—	—
Premature atrial beats	1 (1)	—	—
Atrial fibrillation	1 (1)	—	—

dicative of metabolic or anoxic changes, mechanical alteration (left ventricular stretching), toxic in origin (chronic unconjugated hyperbilirubinemia) or due to other factors?^{33,34} Does their presence increase the risk of arrhythmias during acute or chronic physiologic alterations such as hypoxia, acidosis, hypokalemia, etc?³⁵ Eleven of the 13 patients with arrhythmias also had NS-ST-T abnormalities, but the converse was not true, and the rhythm disturbances recorded for this study were minor.

Men had higher hemoglobin and hematocrit levels, wider QRS intervals, and a higher incidence of LVH, while a significantly higher percentage of women had normal electrocardiograms, compared with men. Are women somehow selectively protected from ECG abnormalities of SCD, or are men predisposed to earlier development of such changes? Does the higher incidence of sinus tachycardia noted in women have significance?

The presence of systemic hypertension in only one patient, who had chronic renal failure, indicates that the incidence of essential hypertension in SCD may be far below that expected in a black population without SCD.^{36,37} It is possible that the known decreased systemic peripheral vascular resistance associated with severe anemia accounts for the apparent decreased prevalence of hypertension in SCD patients.^{38,39}

Patients with systolic murmurs had more severe anemia and paradoxically slower heart rates. Brannon et al⁴⁰ and others⁴¹⁻⁴³ have noted an increase in cardiac output in chronic anemia patients with hemoglobins of 7 g/dL or less, and it has been found that SCD patients generally have an increased cardiac output that may account for some of the cardiac findings.²⁷ An increased stroke volume with increased left ventricular outflow tract turbulence could be the mechanism of the systolic murmurs, although anemia-induced cardiac dilation with mitral regurgitation is an equally plausible explanation.⁴⁴ Mechanisms by which ventricular function may be compromised in the presence of severe anemia are clearly applicable to this patient group.⁴⁵

In summary, this study provides additional data on the incidence of ECG abnormalities in adults with sickle cell disease and these findings indirectly support the need for further correlative studies of pathophysiological mechanisms. Moreover, the frequency of "pseudo-congestive heart failure" findings on the chest x-ray films, without the overt symptoms or physical findings of frank congestive heart failure, indicates the need for careful assessment of the hemodynamic status of these anemic patients, particularly during acute illnesses.

Acknowledgment

Supported in part by grant No. 15162 and contract No. 1-HV72970 from the National Heart, Lung, and Blood Institute.

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