Electrocardiograms and M-mode echocardiograms were obtained prospectively from 72 patients with hemoglobin SS (n = 55) or SC (n = 17) disease to assess the prevalence of abnormal Q waves in sickle cell disease and to determine if such Q waves could be explained by, or related to, echocardiographically determined anatomic or functional abnormalities. The mean age (± SD) of the population under study was 28 ± 9 years, and the mean hematocrit reading was 28 ± 5 percent; 43 male and 29 female patients were evaluated. No patient had a history of systemic arterial hypertension, valvular heart disease, or congestive heart failure. Abnormal septal Q waves (amplitude ≥ 0.30 mV; duration ≥ 29 msec) were noted in leads V₆, V₇, or V₈ in 15 of 72 patients, and 50 percent (36 of the population under study demonstrated echocardiographic voltage changes consistent with left ventricular hypertrophy. M-mode echocardiography showed that 29 of 72 patients had a thickened interventricular septum (≥ 1.2 cm), 16 of 72 had an abnormally thickened left ventricular posterior wall (≥ 1.2 cm), and 31 of 72 had increased left ventricular mass (> 215 g). The prevalence of electrocardiographic and echocardiographic abnormalities was not significantly different between patients with hemoglobin SS and SC disease. Septal excursion was decreased in 11 of the patients, and global left ventricular function (percent fractional shortening) was slightly decreased in three patients. Regional wall motion was normal in all 72 patients. Six percent (four) of the patients met echocardiographic criteria for asymmetric septal hypertrophy. Linear regression analysis yielded significant positive correlations between septal dimension (r = 0.38; p < 0.001) and left ventricular mass (r = 0.37; p < 0.005) when each was compared with Q-wave amplitude. A significant negative correlation (r = 0.40; p < 0.001) was noted between hematocrit reading and Q-wave amplitude. We conclude that abnormal septal Q waves are common in sickle cell disease and are related, in part, to septal thickness, as well as left ventricular mass and degree of anemia.

Cardiovascular manifestations are a prominent component of sickle cell hemoglobinopathy. Non-specific electrocardiographic changes are common in sickle cell disease and have been recognized for more than three decades.¹⁵ Left ventricular hypertrophy is the most frequently reported electrocardiographic abnormality and is seen in 50 to 80 percent of the patients. Other abnormalities which have been noted include first-degree atrioventricular block, nonspecific ST-segment and T-wave changes, and right ventricular hypertrophy; however, echocardiographic abnormalities have not been found to be predictive of clinical findings of cardiac dysfunction.¹

Recent echocardiographic studies of patients with sickle cell disease have demonstrated the presence of cardiac chamber enlargement in some patients and have presented evidence of increased left ventricular mass and increased interventricular septal width.⁶⁻⁸ Echocardiographic evidence of contractile dysfunction (abnormal ejection fraction or velocity of circumferential fiber shortening) is unusual; however, scintigraphic studies of small populations of patients suggest that sickle cell hemoglobinopathy may be associated with exercise-induced right or left ventricular dysfunction.¹⁰⁻¹¹

Postmortem studies have demonstrated gross cardiac anatomic abnormalities and microscopic changes suggestive of microinfarction and myocardial fibrosis, presumably the result of microvascular occlusion by sickled erythrocytes;¹² however, such postmortem studies are limited to a selected subset of patients with sickle cell disease, i.e., those with the most severe disease, those with lethal complications, and those with lethal associated diseases not related to sickle cell hemoglobinopathy. Nonetheless, such studies have given rise to the term, “sickle cell cardiomyopathy.”¹³

Patients with sickle cell disease who have prominent Q waves are frequently referred for evaluation of

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CHEST / 88 / 4 / OCTOBER, 1985 543
ischemic heart disease, "organic heart disease," or so-called sickle-cell cardiomyopathy. To our knowledge, only one previous study specifically reported Q-wave findings in a large series of patients with sickle cell hemoglobinopathy. Q-wave amplitudes up to 0.52 mV were seen in the lateral precordial leads, but the authors did not address their origin or clinical significance. Large-amplitude Q waves of short duration (≤40 msec) are also frequently encountered in hypertrophic cardiomyopathy and have been ascribed to depolarization of the hypertrophied interventricular septum. The term, "septal Q waves," has been used to describe such Q waves.

The purpose of this investigation was to determine the prevalence, origin, and clinical significance of prominent septal Q waves in patients with sickle cell disease.

**Materials and Methods**

**Identification and Selection of Patients**

Eighty-one patients with hemoglobin SS or SC disease were identified by reviewing the hemoglobin electrophoresis file maintained by the Hematology Division of the Department of Medicine and Department of Pathology at Los Angeles County Harbor-UCLA Medical Center. All hemoglobin electrophoresis profiles performed between Jan 1, 1970 and Dec 31, 1983 were available for review. Hemoglobin pattern was determined in all patients by cellulose acetate electrophoresis and, in some instances, by citrate agar electrophoresis, performed in accordance with standard methods.

One patient with documented chronic systemic arterial hypertension, one patient with chronic renal failure, and two patients with rheumatic valvular heart disease were excluded from further study. All excluded patients were identified during preliminary review of the charts. The remaining 77 patients were contacted, and 72 agreed to participate in the study. No studied patient had a history of hypertension or had sought medical attention for dyspnea on moderate exertion, declining exercise tolerance, or pedal edema. Patients were specifically questioned regarding symptoms suggestive of typical angina pectoris, acute myocardial infarction, or congestive heart failure. No studied patient related such a history. A thorough physical examination was performed in all patients. All patients had an automated determination of hematocrit reading and hemoglobin level performed within two weeks of electrocardiographic and echocardiographic assessment. A retrospective review of charts confirmed that the hematocrit reading during study was comparable to hematocrit readings obtained during the 12 months preceding the study. The ECGs and echocardiograms were obtained when patients were asymptomatic.

**Echocardiography**

After informed consent was obtained in accordance with institutional guidelines, all patients underwent M-mode echocardiographic evaluation in the left semilateral decubitus position with the transducer placed at the left sternal border. A 2.25-MHz transducer (Irex System II) or a 3.0-MHz transducer (Advanced Technology Laboratory Mark III) was used for echocardiographic studies.

All measurements except left atrial dimension and aortic diameter were made at the level of the chordae of the mitral apparatus. The end-diastolic measurements for cavity size and wall thickness were taken at the onset of the QRS complex of the simultaneously recorded ECG using the leading-edge method. Systolic measure-

ments of left ventricular internal dimension, interventricular septal thickness, and left ventricular posterior wall thickness were performed at the peak of posterior wall motion. The left atrial dimension was measured at the end of ventricular systole at the level of the aortic valvular leaflets. The percentage of fractional shortening of the left ventricle was calculated using a standard formula. Left ventricular mass was calculated from separate measurements according to the method of Devereux and Reichek. A calculated value exceeding 215 g was considered abnormal. Asymmetric septal hypertrophy was diagnosed if the end-diastolic septal-to-posterior wall thickness ratio exceeded 1.5 and the absolute septal thickness was greater than 1.4 cm.

All echocardiograms obtained from the population studied were reviewed in conjunction with an additional 100 M-mode echocardiograms randomly chosen from the files of the noninvasive cardiac laboratory. In all, 172 echocardiograms were submitted to three of the investigators for blind review. Differences in measurements and assessment of septal and wall motion were resolved by reevaluation and consensus.

**Electrocardiography**

Conventional three-channel 12-lead ECGs were obtained from all patients immediately prior to M-mode echocardiographic study. No studied patient was receiving quinidine, procainamide, or other medication which produces known effects on the surface ECG. Measurements of the R-R interval, P-R interval, QRS duration, Q-wave duration, and corrected Q-T interval were made. A P-R interval of less than 210 msec, a QRS duration of less than 100 msec, and a corrected Q-T interval of less than 480 msec were considered normal. Left ventricular hypertrophy was diagnosed if conventional QRS precordial voltage criteria were met (Sv1 + Rv5 or Rv6 ≥3.5 mV). The depth and duration of Q waves seen in lateral precordial leads V2 to V6 and in standard limb leads 2, 3, and aVF were measured by three of the investigators. Q waves in one or more of these leads which were 0.30 mV or more in amplitude but 29 msec or less in duration were considered to be "deep" or "abnormal" septal Q waves. Q waves of 40 msec or more in duration were considered to be infractional Q waves.

A computer-aided survey of 39,603 consecutively recorded ECGs at our institution over a two-year period (1981 to 1983) was undertaken to provide an estimate of the prevalence of abnormal septal Q waves in a general hospitalized clinical population. Criteria for computerized selection and identification were limited to age (>10 years) and Q-wave amplitude (≥0.30 mV) and duration (≥29 msec). Race, sex, medical history, and diagnosis were not included in the computer program for selection.

**Analysis of Data**

All values are reported as the mean ± SD. When indicated and appropriate, statistical differences were assessed using the two-tailed unpaired Student's t-test or χ² test. Linear regression analysis was used to assess correlations between electrocardiographic measurements, echocardiographic findings, and the severity of anemia (hematocrit). A p value of 0.05 or less was considered statistically significant.

**Results**

**Population of Patients**

The population under study consisted of 55 patients homozygous for hemoglobin S and 17 patients with hemoglobin SC; there were 43 male and 29 female patients. The mean age was 28 ± 9 years (range, 10 to 60 years), and eight patients (11 percent) were more than 40 years of age. The mean hematocrit reading of
the 72 patients was 28 ± 5 percent (range, 15 to 44 percent). The mean age of hemoglobin SS patients was 29 ± 9 years and that of hemoglobin SC patients 26 ± 8 years (difference not significant; two-tailed Student’s t-test applied to unequal sample sizes). The mean hematocrit reading of hemoglobin SS patients was 26 ± 3 percent and that of hemoglobin SC patients 35 ± 4 percent (p<0.001).

The Electrocardiogram

Only seven of the patients (10 percent) had no Q wave in the evaluated inferior and precordial electrocardiographic leads. Sixty-nine percent (50) of the patients had a Q wave of 0.05 to 0.29 mV. Q-wave patterns consistent with our definition of “deep” or “abnormal” septal Q waves were seen in one or more of the lateral precordial leads in 21 percent (15/72) of the population studied (Fig 1). Two (13 percent) of these 15 patients had hemoglobin SC, and 13 (87 percent) had hemoglobin SS. The prevalence of abnormal septal Q waves in patients with hemoglobin SS (13/55; 24 percent) was not significantly different from that in patients with hemoglobin SC (2/17; 12 percent) (χ²=1.732; not significant). Only two of these 15 patients had a Q wave of larger amplitude in a measured standard limb lead (lead 3) than in leads V₅ to V₆; however, in these two cases, the Q wave in lead V₆ also conformed to our criteria for abnormal septal Q wave. Of the 72 patients, none had a Q-wave duration in the inferior limb leads or lateral precordial leads suggestive of myocardial infarction (ie, Q-wave duration ≥ 40 msec). Mean Q-wave amplitude (measured in the lateral precordial leads) for the population with sickle cell disease was 0.21 ± 0.18 mV.

The computer-aided survey of 39,603 consecutively recorded ECGs obtained from the computer disc files of our institution yielded only 77 ECGs (0.19 percent) which conformed to our definition of abnormal septal Q waves. Subsequent review of charts revealed that 18 (23 percent) of the 77 patients were black, and eight (44 percent) of these black patients had sickle cell hemoglobinopathy. Six of the remaining black patients had clinical findings, other electrocardiographic findings, serum enzyme changes, or noninvasive cardiac diagnostic studies which were compatible with ischemic heart disease or definite myocardial infarction.

Fifty percent of the population with sickle cell disease (36/72) met the selected electrocardiographic voltage criteria for left ventricular hypertrophy. Twenty-seven of these patients had hemoglobin SS, and nine had hemoglobin SC. The prevalence of left ventricular hypertrophy in patients with hemoglobin SS and SC was not significantly different (χ² = 0.077). Thirteen (87 percent) of the 15 patients with abnormal Q waves also had abnormalities of precordial electrocardiographic voltage consistent with left ventricular hypertrophy.

Nonspecific ST-segment and T-wave abnormalities were seen in 58 percent (42) of the studied population. Other electrocardiographic abnormalities were infrequent and included first-degree atrioventricular block in 7 percent (five patients), a prolonged QRS duration.
in 6 percent (four), and a prolonged corrected Q-T interval in 11 percent (eight). Six percent of the studied population had electrocardiographic changes consistent with right ventricular hypertrophy (R/S ratio in lead V1 ≥1). No patient had a right or left bundle-branch block pattern.

M-mode Echocardiographic Findings

M-mode echocardiographic observations are summarized in Table 1. The left ventricular end-diastolic dimension was normal in 51 patients and increased in 21 (29 percent). Right ventricular internal dimension was enlarged in 22 patients (31 percent). Nine (13 percent) of the patients had increased left and right ventricular internal dimensions. Mean interventricular septal dimension of the studied population was 1.13 ± 0.27 cm. Left ventricular percent systolic thickening (percent fractional shortening) was decreased in three patients (4 percent). In two of these patients, percent fractional shortening was 23 percent and in one.

Table 2—Electrocardiographic and Echocardiographic Correlates in Hemoglobin S Disease*

<table>
<thead>
<tr>
<th>Dependent Variable</th>
<th>Independent Variable</th>
<th>Correlation Coefficient</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q-wave amplitude</td>
<td>Hematocrit</td>
<td>-0.40</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV mass</td>
<td>Hematocrit</td>
<td>-0.35</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Q-wave amplitude</td>
<td>LV mass</td>
<td>0.37</td>
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</tr>
<tr>
<td>Q-wave amplitude</td>
<td>IVS</td>
<td>-0.37</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Q-wave amplitude</td>
<td>IVS</td>
<td>0.38</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*LV, Left ventricular; IVS, interventricular septum; and RV, right ventricular. Note LV and RV end-diastolic and LV end-systolic dimensions represent measured internal diameters.

Four (6 percent) of the 72 patients met echocardiographic criteria for asymmetric septal hypertrophy (septal-to-posterior free wall thickness ratio >1.5; septal thickness ≥1.4 cm). Systolic anterior motion of the mitral apparatus was not present in any of these four patients.

Electrocardiographic and Echocardiographic Correlates

Twelve (80 percent) of the 15 patients with abnormal septal Q waves had an interventricular septal end-diastolic dimension of 1.2 cm or more. Ten (67 percent) of the 15 patients with abnormal septal Q waves had increased left ventricular mass by echocardiographic criteria. Only two (13 percent) of the 15 patients with abnormal septal Q waves had normal end-diastolic septal dimensions and normal echocardiographic left ventricular mass. In nine (60 percent) of the 15 patients, both end-diastolic septal dimension and left ventricular mass were increased. Five (33 percent) of the 15 patients with abnormal septal Q waves did not meet echocardiographic criteria for increased left ventricular mass.

Table 2 summarizes calculated correlation coefficients (r values) and their statistical significance for selected echocardiographic measurements (septal dimension and left ventricular mass), Q-wave amplitude (deepest Q wave in lead Vs, Vs, or Vd), or degree of anemia (hematocrit reading). Q-wave amplitude was correlated directly with interventricular septal thickness and left ventricular mass and inversely related to hematocrit reading. Left ventricular mass and interventricular septal thickness were both inversely correlated with hematocrit reading.

Discussion

The present study demonstrates that large-amplitude narrow Q waves, so-called abnormal "septal" Q waves, are common in patients with sickle cell disease. Abnormal "septal" Q waves (≥0.30 mV in amplitude; ≤29 msec in duration) were present in one or more of the lateral precordial electrocardiographic leads (Vs to Vd) in 21 percent (15) of our population of patients homozygous for hemoglobin SS or with hemoglobin SC. Q-wave duration was less than 30 msec in all patients and thus did not conform to accepted criteria for infarctional Q waves (≥40 msec).29

Small, narrow Q waves are physiologic and are the result of septal depolarization.29 In a study of 100 normal adults, Cooksey et al29 noted that 60 percent of a normal population had a Q wave in lead V5, and 75 percent had a Q wave in lead V6; however, in the normal population the mean Q-wave amplitude was...
only 0.03 mV. Abnormal “septal” Q waves are likewise uncommon in the general hospitalized population. Only 0.17 percent of 39,603 ECGs recorded from our hospitalized clinical population (exclusive of patients with sickle cell disease) demonstrated such abnormal “septal” Q waves. Thus, large-amplitude narrow Q waves are rare in normal subjects and in the general hospitalized population, while they are frequently observed in patients with sickle cell hemoglobinopathy who do not have coexisting evidence for myocardial infarction or ischemic heart disease.

Abnormal “septal” Q waves have been described in other cardiac conditions such as hypertrophic cardiomyopathy. The large Q waves noted in hypertrophic cardiomyopathy have been ascribed to depolarization of the massively hypertrophied interventricular septum; however, the genesis of abnormal septal Q waves in patients with hypertrophic cardiomyopathy is unclear, since not all such patients have abnormal septal Q waves. Electrocardiographic and echocardiographic studies of such patients indicate that 23 to 32 percent have a Q wave in precordial leads V5, V6, or V1 that is 0.1 mV or more7 and that abnormal “septal” Q-wave patterns are not directly related to interventricular septal dimension. Although the mean interventricular septal dimension for the population with sickle cell disease was at the upper limit of normal and four patients met echocardiographic criteria for asymmetric septal hypertrophy, eg, left ventricular cavity size.

In our study a significant and moderately predictive correlation was demonstrated between Q-wave amplitude and echocardiographically determined interventricular septal dimension and left ventricular mass. Our findings suggest that abnormal “septal” Q waves in patients with hemoglobin S disease are related to both interventricular septal thickness and the degree of left ventricular hypertrophy. The correlation between Q-wave amplitude and septal dimension may, in fact, have been affected by the extent of hypertrophy of the free wall of the left ventricle. The forces of depolarization in free wall hypertrophy may attenuate or “cancel” the electrocardiographic manifestations of septal depolarization.

In this study, Q-wave duration in patients with sickle cell disease did not conform to accepted standards for myocardial infarction. Our clinical, electrocardiographic, and echocardiographic findings are in agreement with other investigations employing noninvasive cardiac diagnostic techniques. Percent fractional shortening, regional wall motion, and global left ventricular function were normal or nearly normal in all of our patients. Both our study and pathologic studies7 suggest that clinically significant myocardial necrosis or fibrosis are rare in patients with sickle cell disease uncomplicated by arterial hypertension or valvular heart disease.

A significant inverse correlation was noted between Q-wave amplitude and measured hematocrit reading. This is perhaps not surprising, since the chronic anemic state, characterized by low oxygen delivery to the peripheral tissues, produces a compensatory increase in cardiac output over time by expansion of plasma volume. This compensatory mechanism is thought to lead to left heart diastolic volume overload and myocardial hypertrophy. We noted an echocardiographic pattern of left ventricular overload in 29 percent (21) of our population with sickle cell disease, and 43 percent (31) of the studied patients met echocardiographic criteria for increased left ventricular mass. Our findings confirm that chronic anemia and its associated high-output state is a stimulus for septal and left ventricular hypertrophy and suggest that large-amplitude narrow Q waves may be an electrocardiographic manifestation of high-output hypertrophy (diastolic overload state).

We conclude that large-amplitude Q waves (≈0.30 mV, ≈29 msec in duration) are common in patients with hemoglobin S disease and are in part, but not exclusively, of septal origin. Their presence or absence in a patient with hemoglobin S disease correlates with septal dimension, left ventricular mass, and degree of anemia. These prominent Q waves do not appear to be due to infarction as determined by clinical history and analysis of ventricular wall motion.

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John P. Wyatt Travelling Fellowship in Environmental Pathology

The University of Kentucky and the Kentucky Tobacco Research Board announce the John P. Wyatt Travelling Fellowship in Environmental Pathology.

- Awards will be made for travel and associated costs to individuals studying environmentally-caused diseases. Preference will be given to applications from individuals interested in the study of respiratory conditions. Applications should include the stated purpose and significance of study, justification of budget for travel, and a curriculum vita.
- One award for one thousand dollars ($1,000.00) will be granted and may be applied for travel anywhere in the world.
- Applications will be reviewed by a committee of three, consisting of one each from the University of Kentucky, the Kentucky Tobacco Research Board, and the Fleischner Society. Applications should be sent to W. C. Royster, Vice Chancellor for Research and Dean of the Graduate School, University of Kentucky, Lexington, Kentucky 40506.
- Deadline for applications is December 1, 1985. Award will be effective January 15, 1986 and may be used anytime within one calendar year of award date.

548

Abnormal Septal Q Waves in Sickle Cell Disease (Lippman et al)