MYOCARDIAL INFARCTION IN SICKLE CELL DISEASE

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Vasculo-occlusive crisis with organ infarctions occur in sickle cell disease (SCD). However, heart infarction is not commonly reported. We reviewed 19 cases of documented myocardial infarction (MI) in SCD patients. The true incidence may be higher because the diagnosis was often made at autopsy and was overshadowed during life by other musculoskeletal symptoms. Electrocardiography is frequently unhelpful. Skeletal muscle enzymes confound serum cardiac enzyme interpretation. The mechanism of MI in SCD is not exactly known, as coronary angiography is usually normal. MI frequently occurs in association with hypoxia, cor pulmonale, anemia, sepsis, acidosis, and renal failure. The aim of this article is to increase awareness for this complication and to prompt prospective studies to look at treatment strategies for myocardial infarction in SCD. (*J Natl Med Assoc.* 2002;94:448–452.)

Kew words: myocardial infarction ♦ sickle cell disease ♦ Nitrates ♦ Magnesium

Vasculo-occlusive crises are well-known complications of sickle call diseases (SCD). Internal organ infarctions secondary to vascular obstruction by sickling cells commonly affect bone, lung, spleen, central nervous system, retina, and kidney.[1,2] The cardiopulmonary complications of SCD include ventricular dilatation and hypertrophy, congestive heart failure, pulmonary hypertension, and cor pulmonale.[3,4] However, sickling in the heart resulting in ischemia or infarction is not commonly reported. In fact, some reports describe the heart as resistant to the effects of sickling.[5] Other studies describe "super normal" coronaries at autopsy, which are patent and large with less atherosclerotic lesions than expected from age-matched peers.[6,7] Data from autopsies in U.S. soldiers killed in Korea or Vietnam indicate far more coronary athersclerosis in presumably healthy soldiers than in patients with sickle cell anemia of comparable age.[7] Moreover, SCD patients are viewed to be of lower risk for ischemic heart disease because they often have low serum cholesterol[8] and die at a younger age from noncardiac causes. However, many case reports and autopsy studies clearly show that myocardial ischemia and infarction occurs in SCD and can contribute significantly to morbidity and mortality.[7,9–15]

METHODS

Inclusion and Exclusion Criteria

We reviewed the literature for reported cases of myocardial infarction (MI) in SCD. We restricted our review to studies and case reports that: (1) involved patients with SCD (SS or SC

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Table 1. Myocardial Infarction in Sickle Cell Disease

Author (Reference)	Study type	Total number of patients	Number with MI	Chest pain	ECG (number of patients with findings)	Cardiac Enzymes	Coronary arteries	Other associated factors (number of patients)
Martin 1996 (9)	Autopsy	72	7	6	Q-wave (2)	—	Normal	Cor pulmonale and hypoxia (3)
Norris 1991 (10)	CP	19	4*	19	ST-T changes (4)	2	—	—
Saad, 1990 (11)	CR	1	1	1	Q, ST (1)	—	Normal	Hypoxia, severe anemia (1)
McCormick, 1988 (13)	CR	1	1	1	Q, ST (1)	—	Stenosis	Cor pulmonale, hypoxia, anemia, renal failure (1)
Martin, 1983 (12)	CR	1	1	1	Q, ST (1)	—	Normal	Anemia (1)
Barrett, 1984 (7)	CR	2	2	2**	Q-wave (1), ST (2)	—	Normal	Infection (1), anemia (1)
Woodruff, 1970 (15)	CR	1	1	1	Postero-septal MI***	—	—	Infection (1)
Rubler, 1967 (35)	CR	1	1	1	—	—	Normal	—
Uzsoy, 1964 (36)	Autopsy	9	1	1	Posterior MI***	—	Normal	—
Total		107	19	33	14	2	1	8

CP: Clinical prospective. CR: Case report.
*Four patients with probable MI as suggested by segmental wall motion abnormalities on radionuclide imaging, and 7 with myocardial ischemia.
**One patient had chest pain; the second had epigastric pain that was considered gastritis.
***Details of ECG findings are unavailable.

Sickle cell disease) without other hemoglobinopathies; (2) MI was diagnosed either by (a) postmortem autopsy examination, (b) a constellation of clinical picture, ECG changes along with evidence of segmental wall motion abnormality on a noninvasive heart imaging technique. We exclude case reports of infants or children younger than 15 years that did not describe the coronary anatomy to rule out the possibility of congenital anomalies of the coronary arteries.[16,17]

Search Strategies and Data Abstraction

The two authors independently performed a MEDLINE search to find all suitable studies. A search strategy using the combined Medical Subject Headings "Sickle cell disease" and "Myocardial infarction" was used. No time or language limit was applied. The search terms "Sickle cell anemia," "Sickle cell crisis," and "Myocardial ischemia" were also included. A separate search using the Medical Subject Headings of "Sickle cell disease" alone, with a time limit of 1999 through 2000, was also conducted. The titles and abstracts were reviewed to identify relevant articles. All review articles on management of sickle cell crisis or acute chest syndrome, with a time limit from 1997 through 2000, were reviewed to identify any relevant recommendations. Reference lists from reviews and selected articles were examined to identify relevant articles. We did not contact authors for additional details of studies.

RESULTS

Table 1 summarizes data from 19 cases of MI in SCD identified in the literature.

DISCUSSION

The exact mechanism of MI in SCD is unknown, although the combination of the stress of anemia—rheological, morphological, and

biochemical effects of the sickle cells themselves—and platelet abnormalities may play a role. Sickled cells can stack and agglutinate into obstructive masses within arteries and become further enmeshed with circulating platelets to form obstructive masses. The platelets in SCD may have an intrinsic or primary abnormality.[4,18,19] Several studies report decreased platelet survival during vasculo-occlusive crisis.[20–22] Thromboxane released from sequestrated platelets in the coronary vasculature may play a role in myocardial ischemia and necrosis by inducing vasospasm. Rheological factors of altered viscosity, altered membrane flexibility, and aggregation of the red blood cells in sickle cell disease may cause coronary vascular obstruction leading to ischemia and infarction.[23]

James[19] suggests that the mechanism of myocyte death in SCD is by apoptosis rather than by myocardial necrosis. Cardiac myocytes typically rupture during necrosis but not during apoptosis, although death by either process leaves the myocytes equally dead. Accordingly, enzymatic serum markers may not be useful in myocardial death by apoptosis, as cells do not rupture to release enzymes.

Difficulties in the Diagnosis of Myocardial Infarction in SCD

Although 19 cases of myocardial infarction in SCD were identified in this search of the literature, the true number may exceed what is reported in the literature, as the diagnosis is frequently missed and occasionally made only at autopsy.[7,9] Certain features of vasculo-occlusive crisis may confound the clinical picture and laboratory investigation of MI in SCD. Chest pain, a hallmark in diagnosing MI, is usually attributed to the pain of vasculo-occlusive crisis. Rib infarction may cause chest pain with muscular or pleuritic characteristics. Epigastric pain because of nonsteroidal anti-inflammatory medications may occur. This noncardiac pain may overshadow the pain of myocardial ischemia. Given the low-risk profile of these patients, ischemic pain is often missed. On the other hand, when ischemia was present in SCD patients, chest pain was reported in the majority of the patients (Table 1). This observation should alert clinicians that myocardial ischemia should be considered whenever a SCD patient presents with chest pain.

An electrocardiogram (ECG) is often unhelpful, as nonspecific ST-T wave changes commonly exist in SCD.[4,7,24] In a review of 108 patients with SCD,[7] only 41% had a normal ECG, 18.5% had nonspecific ST-T wave changes, 36.8% had left ventricular hypertrophy, and 2.7% had myocardial infarction. Martin and colleagues autopsied 7 patients with SCD who had MI. Only 2 ECGs had characteristics of MI, and the rest had nonspecific ST-T wave changes. Norris and colleagues[10] investigated 20 SCD patients (19 patients with SCD and 1 patient with sickle-B thalassemia) who presented with chest pain. Eleven patients were found to have ischemia or infarction by other noninvasive tools. None of these patients had ECG changes typical of MI, but serial ST-T wave changes were suggestive of ischemia or infarction. ECG is thus not a sensitive tool to rule out MI in SCD patients presenting with chest pain.

The role of serum cardiac enzymes in the diagnosis of MI in SCD is shown in Table 1. Norris and colleagues found that only 2 of 4 SCD patients with myocardial infarction had cardiac enzyme abnormalities suggestive of infarction.[10] Other series of SCD patients with MI (Table 1) report that cardiac enzymes were either not done or were done beyond the time frame for MI diagnosis.[7,11–14] Moreover, frequent intramuscular injections of analgesics in SCD patients with vasculo-occlusive crisis further confound enzyme level and their interpretation. Conventional serum cardiac enzymes measurements (CK, LDH, SGOT) were not helpful in the diagnosis of MI in SCD. Cardiac troponin T has been reported to be nonspecifically increased in SCD with skeletal muscle damage using earlier generation reagents.[25] To our knowledge, there is no published data about the use of troponin I or newer genera-

tions of troponin T in evaluating chest pain in SCD.

Coronary Angiography. In the vast majority of reported cases of MI in SCD, coronary arteries were found patent and occasionally described as "super normal" coronaries.[6] Only 1 patient in the 107 patients shown in Table 1 had coronary epicardial disease.[13] Although the patient had significant coronary stenosis, it was a result of endothelial proliferation and fibrosis and not of atherosclerotic origin.

Features Associated with Myocardial Infarction in SCD. Many reports show that MI takes place in SCD patients in the context of other SCD complications and acute illnesses. Martin and colleagues found that 3 of 7 patients with MI had hypoxia or cor pulmonale. Similar findings are described in other case reports,[11,13] along with fulminant infections,[7] acidosis, and renal failure.[13,15] Anemia was a common feature in SCD patients who sustained MI. Variable levels of hemoglobin, ranging from 2.9 to 9.3 g, were reported in these cases. The decrease in hemoglobin level rather than the absolute hemoglobin level itself seems to be associated with myocardial infarction.[7,11,12] Perhaps patients with SCD and chest pain should be risk-stratified for these factors, as well as the traditional risk factors for ischemic heart disease such as age, diabetes, hypercholesterolemia, smoking, and strong family history.

Management. There is no data in the literature for management of MI in SCD. Because many SCD patients with sudden death are found to have myocardial infarction at autopsy, and arrhythmias occur during acute vasculo-occlusive crisis,[7,26,27] it seems appropriate that SCD patients with chest pain be admitted to closely monitored beds. They should be promptly hydrated and oxygenated if hypoxic.[28] The role of aspirin, heparin, and beta-blockers, a routine treatment for myocardial infarction, is not known in MI in SCD as, to our knowledge, there is no data in the literature that has assessed the value of these therapies in SCD. Many reports show a favorable in vitro effect of nitric oxide in inhibiting sickle erythrocytes' adherence to endothelium,[29] an initiating event in vasculo-occlusive crisis.[30] Nitric oxide has been successfully used in the treatment of SCD with acute chest syndrome.[31] We suggest that nitrates may be helpful in the management of acute ischemic syndromes in SCD, although further study is needed to prove the efficacy of the oral nitrate in this entity. Magnesium has a controversial role in the management of acute MI in the normal population.[32] Since oral magnesium supplementation may be valuable in SCD in preventing erythrocyte dehydration with a decrease of painful crisis,[33] magnesium may be specifically considered in the management of MI in SCD. No studies in the literature report the use of magnesium in these settings. The role of thrombolytic therapy for patients with MI and SCD is also not reported and warrants further studies, as most of the autopsy studies of MI in SCD did not show obstructive coronary artery disease. The role of exchange transfusion and newer antiplatelet agents, as well as the potential role of antiadhesion therapy,[34] is not known.

CONCLUSION

MI occurs in SCD and should be considered in the differential diagnosis of patients with chest pain. Risk stratification of these patients should primarily consider associated medical conditions such as worsening anemia, hypoxia, cor pulmonale, renal failure, infection, and acidosis. ECG and cardiac enzymes may or may not be helpful. New serum markers of infarction such as troponin I and T may be helpful, but no data are currently available on their utility in this situation. Coronary angiography is usually normal and may not be recommended as a routine procedure in young SCD patients with low conventional risk profiles.

Patients with SCD and chest pain who are suspected of having myocardial ischemia should be admitted to a cardiac monitoring unit. Other associated medical conditions should be promptly managed along with hydration and oxygenation. Further studies are needed to assess the effect of antiplatelet

agents, exchange transfusion, and other conventional modes of management of ischemic heart disease.

REFERENCES

1. Weksler BB. Hematology. In: Andreoli TE, Bennett JC, Carpenter CC, Plum F, Smith LH, eds. *Cecil Essentials of Medicine.* 3rd ed. Philadelphia: WB Saunders Company; 1993:370–372.
2. Mansi I, Al-khunaizi A, Alkhatti A. Bilateral central retinal artery occlusion secondary to sickle cell disease, case report. *Am J Hematology.* 2000;64:79–80.
3. Powars DR. Sickle cell anemia and major organ failure. *Hemoglobin.* 1990;14:573–598.
4. Schulman LN, Braunwald E, Rosenthal DS. Hematological-oncological disorders and heart disease. In: Braunwald E. ed. *Heart Disease: A Textbook of Cardiovascular Medicine.* 5th ed. Philadelphia: WB Saunders Company; 1997:1787–1788.
5. Baroldi G. High resistance of the human myocardium to shock and red blood cell aggregation (sludge). *Cardiologia.* 1969; 54:271–277.
6. Gerry JL, Bulkley BH, Hutchins GM. Clinicopathologic analysis of cardiac dysfunction in 52 patients with sickle cell anemia. *Am J Cardiol.* 1978;42:211–216.
7. Barrett O Jr, Saunders DE Jr, McFarland DE, et al. Myocardial infarction in sickle cell anemia. *Am J Hematol.* 1984; 16:139–147.
8. Cantarow A, Trumper M. *Clinical Biochemistry.* Philadelphia: WB Saunders Company; 1975:142.
9. Martin CR, Johnson CS, Cobb C, et al. Myocardial infarction in sickle cell disease. *J Natl Med Assoc.* 1996;88:428–432.
10. Norris S, Johnson CS, Haywood LJ. Sickle cell anemia: does myocardial ischemia occur during crisis? *J Natl Med Assoc.* 1991;83:209–213.
11. Saad STO, Arruda VR, Junqueira OOMD, et al. Acute myocardial infarction in sickle cell anemia associated with severe hypoxia. *Postgrad Med J.* 1990;66:1068–1070.
12. Martin CR, Cobb C, Tatter D, et al. Acute myocardial infarction in sickle cell anemia. *Arch Intern Med.* 1983;143:830–831.
13. McCormick WF. Massive nonatherosclerotic myocardial infarction in sickle cell anemia. *Am J Forensic Med Pathol.* 1988;9: 151–154.
14. Botreau-Roussel P, Drobinski G, Levy R, et al. Infarctus du myocarde et drépanocytose hétérozygote, a propos de 2 cas. *Arch Mal Cœur.* 1977;70:141–147.
15. Woodruff AW. Sickle cell anaemia with complicating coronary infarction. *Proc Roy Soc Med.* 1970;63:1314.
16. De Pontual L, Acar P, de Montalembert M, et al. L'ischémie myocardique: une complication méconnue de la drépanocytose chez l'enfant. À propos de deux observations. *Arch Pediatr.* 1999;6:178–181.
17. Koate P. Pathologie cardiovasculaire dans la drépanocytose. *Bull Acad Natle Med.* 1991;175:1055–1063.
18. Brittain HA, Eckman JR, Swerlick RA, et al. Thrombospondin from activated platelets promotes sickle erythrocyte adherence to human microvascular endothelium under physiologic flow: a potential role for platelet activation in sickle cell vaso-occlusion. [abstract] *Blood.* 1993;81:2137–2143.
19. James TN. Homage to James B. Herrick. A contemporary look at myocardial infarction and at sickle cell disease. *Circulation.* 2000;101:1874–1899.
20. Vandersar A. The sudden rise of platelets and reticulocytes in different sickle cell crisis. *Blood.* 1969;34:733.
21. Gordan A, Breeze G, Mann J, et al. Coagulation fibrinolysis in sickle cell disease. *J Clin Pathol.* 1974;27:485–489.
22. Freedman M, Karpatkin S. Elevated platelet count and megathrombocyte number in sickle cell anemia. *Blood.* 1975;46: 579–582.
23. Chun S, Vsami S, Bertles J. Abnormal rheology of oxygenated blood in sickle cell anemia. *J Clin Invest.* 1970;49:623–634.
24. Karayalcin G, Rosner F, Kim K, et al. Sickle cell anemia—clinical manifestations in 100 patients and review of the literature. *Am J Med Sci.* 1975;269:51–68.
25. Hossein-Nia M, Nisbet J, Merton GK, et al. Spurious rises of cardiac troponin T. *Lancet.* 1995;346:1558.
26. Charache S. Sudden death in sickle cell trait. *Am J Med.* 1988;84:459–461.
27. James TN, Riddick L, Masing GK. Sickle cells and sudden death: morphological abnormalities of the cardiac conduction system. *J Lab Clin Med.* 1994;124:507–520.
28. Johnson WH Jr, McCrary RB, Mankad VN. Transient left ventricular dysfunction in childhood sickle cell disease. *Pediatr Cardiol.* 1999;20:221–223.
29. Space SL, Lane PA, Pickett CK, et al. Nitric oxide attenuates normal and sickle red blood cell adherence to pulmonary endothelium. *Am J Hematol.* 2000;63:200–204.
30. Hebbel RP. Adhesive interactions of sickle erythrocytes with endothelium. *J Clin Invest.* 1997;99:2561–2574.
31. Sullivan KJ, Goodwin SR, Evangelist J, et al. Nitric oxide successfully used to treat acute chest syndrome of sickle cell disease in a young adolescent. *Crit Care Med.* 1999;27:2563–2568.
32. ISIS-4 Collaborative Group. ISIS-4: a randomized factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58,050 patients with suspected acute myocardial infarction. *Lancet.* 1995;345:669–685.
33. De Franceschi L, Bachir D, Galacteros F, et al. Oral magnesium pidolate: effects of long-term administration in patients with sickle cell disease. *Br J Haematol.* 2000;108:284–289.
34. Harlan JM. Introduction: anti-adhesion therapy in sickle cell disease. *Blood.* 2000;95:365–367.
35. Rubler S, Fleischer R. Sickle cell states and cardiomyopathy. *Am J Cardiol.* 1967;19:867–872.
36. Uzsoy N. Cardiovascular findings in patients with sickle cell anemia. *Am J Cardiol.* 1964;11:320–327.