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Myocardial Infarction in Sickle Cell Disease: Use of Translational Imaging to Diagnose an Under-Recognized Problem

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Abstract

Sickle cell disease (SCD) is an inherited disorder in which microvascular occlusion causes complications across multiple organ systems. The precise incidence of myocardial ischemia and infarction (MI), potentially under-recognized microvascular disease-related complications, remains unknown.

The absence of typical atherosclerotic lesions seen in other patients with MI suggests a microvascular mechanism of myocardial injury. Cardiac magnetic resonance (CMR) can demonstrate microvascular disease, making it an appealing modality to assess symptomatic SCD patients. We demonstrate in several dramatic instances how CMR uniquely able to depict cardiac microvascular obstruction in patients with SCD and chest pain, without which the possibility of myocardial injury would almost certainly be otherwise neglected.

Much remains unknown regarding ischemic heart disease in patients with SCD including prevalence, detection and management. Further work to define evaluation and management algorithms for chest pain in SCD and to develop risk assessment tools may reduce sudden cardiac death in this population.

Keywords

sickle cell disease; myocardial infarction; ischemic heart disease; microcirculation; magnetic resonance

Defer no time, delays have dangerous ends.

-William Shakespeare, King Henry VI, part I

INTRODUCTION

Sickle cell disease (SCD) produces considerable morbidity and mortality worldwide. Each year, over 217,000 babies are born with the disease(1, 2), and in the United States, 1 in 500 African-American newborns are afflicted with the disease(3). SCD damages lung, kidney, bone, spleen and central nervous system; microvascular disease serves as the common substrate for these various manifestations.(4) Increased awareness and screening of the disease, use of vaccines against bacterial and viral illnesses, early treatment with antibiotics and adoption of drugs have improved the longevity of patients with SCD as evident by greater survival of children with SCD into adulthood.(5) However, improved survival has brought increased prevalence of cardiopulmonary complications such as pulmonary arterial

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hypertension and its sequelae.(6–8) A less well defined but a potentially catastrophic complication of SCD is myocardial infarction (MI). Notably, Dr. James Herrick who first described the sickled red blood cell in 1910(9) was also one of the first to recognize coronary thrombosis as the cause of MI.(10) This review addresses ischemic myocardial disease as a potentially under recognized source of morbidity and mortality in SCD, proposes new approaches for better identifications and concludes with implications of better detection on management to improve outcomes.

PATHOPHYSIOLOGY OF VASO-OCCLUSION

The genetic defect resulting in sickle hemoglobin (HbS) is a single nucleotide substitution (GTG for GAG) at codon 6 of the β -globin gene on chromosome 11 that results in the replacement of valine for glutamic acid. In addition, numerous genes involved in cell adhesion, inflammation, coagulation, immunity and nitric oxide metabolism among many other processes have been increasingly recognized as contributing to SCD complications(11). When HbS is de-oxygenated, it forms a polymer and causes an alteration in the red cell membrane, producing the sickle shape.(12) This inelastic sickle cell is less deformable and less mobile as it traverses through capillaries. Time to polymer formation is shortened with increasing amounts of HbS in the red blood cell, and increased transit of red blood cells through low oxygen tension vessels promotes sickling. However there is unexplained heterogeneity in the phenotypic expression of the disease in terms of age of onset and severity of disease despite a similar genotypic makeup. Speculation of other measures such as globin cluster haplotype have been proposed to have role in this but only the coinheritance of β -globin gene variant (presence of β -thalassemia) and expression of β -globulin (HbF) are validated to have an ameliorating role in the expression of the disease.

Presence of thalassemia and higher levels of Hb F reduce HbS polymerization. A switch from β to β -globin gene occurs after birth whereby HbF is replaced by HbS. Independent HbF genome wide association studies have identified few loci that have significant effects on the disease expression. Three genes namely, the β -globin gene cluster, gene encoding BCL11A on chromosome 2, genes encoding HB1SL and Myb on chromosome 6 account for ~40% of variation of HbF produced. The proteins encoded play a role in the expression of HbF(13) and ultimately drugs such as hydroxyurea (hydroxycarbamide) that target an increased HbF production were instrumental in treating SCD in adults(14).

Vaso-occlusion is a multifactorial event related to polymerization of HbS, inelastic sickle cells, and endothelial dysfunction. Nitric oxide (NO) produced in endothelium maintains a basal vasodilator tone, inhibits platelet activation as well as transcription of cell adhesion molecules and keeps superoxide free radicals under check through a scavenging pathway. Intravascular hemolysis makes available cell free hemoglobin thus deactivating NO leading to a state of NO resistance. Another consequence of lysis is the release of erythrocyte arginase which converts L-arginine (precursor of NO) to ornithine, depleting the substrate of NO production. Meanwhile there is increased expression of adhesion and procoagulant molecules on red blood cells and endothelium, increased levels of inflammatory cytokines and interactions between sickle cells and leukocytes.(15) The end result, microvascular occlusion is characterized by impaired nitric oxide bioavailability, nitric oxide resistance, and nitric oxide inactivation.(16–18) Impaired nitric oxide bioavailability is central to the endothelial dysfunction seen in sickle cell disease as it results in vasoconstriction, activation of platelets and coagulation, and increased adhesion receptor expression on vascular endothelium, serving as possible targets for therapeutic intervention.(15, 19) (Figs. 1–2)

HISTOPATHOLOGIC EVIDENCE OF MYOCARDIAL INJURY AND SUDDEN CARDIAC DEATH

Myocardial infarction in SCD has been previously described in various case reports and case series (Table 1)(4, 20–32). The first description was an autopsy report by Oliveria and Gomez-Patino.(33) Martin *et al.* evaluated autopsy performed on 72 hearts of patients with SCD and identified lesions meeting criteria for myocardial infarction in 7 of 72 patients (9.7%).(26) While typical myocardial infarction occurs as a consequence of rupture or erosion of a vulnerable atherosclerotic plaque and subsequent thrombosis, myocardial infarction in SCD has not been associated with epicardial coronary atherosclerosis by either autopsy(20) or *in vivo* coronary angiography.(32) This leaves microvascular disease related to vaso-occlusion as the likely cause of myocardial ischemia and injury in these patients.(4)

A large autopsy series of 306 patients that included pediatric patients revealed that death was sudden in 40.8% with a significant high risk of death occurring within 24 hours of hospitalization.(34) Within the hemoglobin-SS subgroup, infectious etiologies caused 61% of deaths. Cardiomegaly was identified in 58% of hearts, with myocardial microinfarcts in 20%. Myocarditis (plausibly leading to arrhythmia) was observed in 5% of cases where infection was deemed responsible for death.

Similar results emerged from Fitzhugh *et al.*(35) who reviewed clinical and autopsy records from patients with SCD. They reported 39 years as the median age of death, with either cardiac or pulmonary issues accounting for 39.5% of deaths. Cardiac arrest with pulseless electrical activity was responsible for 11.6% of fatalities while myocardial infarction was identified in 7%.(35) Notably, there was no significant difference in the percentage of live vs. deceased patients who were previously taking hydroxyurea during the 5-year observation period, suggesting that myocardial disease may proceed despite the other benefits of hydroxyurea. In a 4-decade longitudinal study spanning both pre- and post-hydroxyurea eras, Powars *et al.* reported median survival to be 36.3 years for females and 38.7 years for males.(5) The pre-hydroxyurea data of Platt *et al.*(36) surprisingly reported greater longevity, raising the possibility of selection bias.

Although relation between coronary artery disease and sudden cardiac death is well established in the general population, the absence of coronary artery atherosclerotic disease in SCD suggests that microvascular obstruction, hypoxemia and alteration in vascular flow lead to myocardial injury and be a substrate for fatal arrhythmias in these patients. The landmark Framingham study of risk factors and cardiovascular events identified a 3- to 6-fold increase in sudden death in patients with left ventricular hypertrophy (LVH).(37) Data from the Cooperative Study of Sickle Cell Disease analyzing 3800 patients confirmed LA and LV enlargement in SCD.(38) LVH is disproportionately prevalent in patients with SCD, and it is believed to be a consequence of increase cardiac work due to anemia(39) as well as impedance to flow from narrowing of vessel due to intimal hyperplasia, mediated by growth factors.(40) LVH and subendocardial ischemia can act as an arrhythmogenic substrate. Further, hypertrophied myocardium itself via abnormal myocyte architecture and fibrosis can serve as a nidus for ventricular reentrant arrhythmias. The occurrence of atrial and ventricular arrhythmias during crisis and hemolysis further supports microvascular obstruction as a possible underlying mechanism.(41)

DIAGNOSTIC TECHNIQUES TO DETECT MYOCARDIAL ISCHEMIA OR INFARCTION

Commonly used diagnostic tools in reported *in vivo* cases of SCD-associated MI have included electrocardiography, cardiac enzyme elevation, infarct scar by imaging. However,

the diagnosis of MI remains infrequently considered during clinical assessment of symptomatic patients experiencing SCD.(42) This may reflect relatively low incidence as well as inconsistent utilization and sensitivity of various diagnostic modalities. Of course, without appropriate clinical suspicion, even the most sensitive tests may not be used to recognize MI in SCD.

Electrocardiography (ECG)

Increased in R wave voltage and secondary ST-T wave changes are commonly present on routine 12-lead ECG due to LV enlargement that, in turn, occurs in response to long-standing anemia. Distinguishing repolarization abnormalities due to acute myocardial ischemia from those resulting from LV enlargement may be facilitated by comparison to prior tracings and appreciation of the magnitude and direction of ST-T wave changes. In one review, Q waves and ST-T abnormalities were identified in 14 of 19 cases of SCD-associated MI.(43) Less equivocal is regional ST elevation, which should prompt consideration of myocardial injury when present (Figs 3–4). Given the nonspecific nature of most ECG abnormalities in patients with SCD, further corroboration of myocardial ischemia and infarction by other testing may often be needed.

Biomarkers

Cardiac biomarkers are well-established, widely available tools in making the diagnosis of myocardial injury.(44) Measurement of otherwise undetectable intra-myocyte proteins in the blood such as troponin, creatine kinase and myoglobin typically indicates irreversibly damaged myocardium.(44) Despite the versatility of this test, there is paucity of data with regards to its use in identifying myocardial cell injury in sickle cell disease patients. In 32 patients admitted with sickle cell crisis, Aslam *et al.* measured troponin-I levels at baseline, 6 and 12-hours post-admission.(45) Only 2 of the 32 patients had a positive test indicating myocardial injury (with echocardiographic evidence of LV dysfunction in 1 patient) suspected to be due to microvascular obstruction and both the patients exhibited features of acute chest syndrome. In a subsequent report, Lippi *et al.* observed elevation of the MB isoform of creatine kinase but no troponin-T elevation during sickle cell crisis (without acute chest syndrome) in comparison to levels during stable disease state.(46) Although limited in their sample size, these reports support the notion that myocardial injury need not necessarily accompany every sickle cell crisis. But when it does, the use of a widely available tool with high sensitivity and specificity such as cardiac biomarker assay (Troponin-I, Troponin-T) renders with ease a clinician the ability to identify and initiate treatment averting significant morbidity and mortality.

Echocardiography

Pulmonary hypertension, a disease characterized by endothelial and smooth muscle proliferation of small pulmonary arteries has been reported as a frequent complication of SCD with a prevalence of ~30%. (47, 48) Echocardiographic documentation of a tricuspid valve jet velocity of 2.5m/sec or above generally defines pulmonary hypertension (Mean pulmonary artery pressure >25mmHg), but has a low positive predictive in SCD when compared to the gold standard of right heart catheterization.(49) The role of increased LV mass and diastolic dysfunction as an independent risk factor of mortality(50) emphasize the significance of routine echocardiographic assessment of SCD patients in an effort to provide risk stratification.

Stress echocardiography may be used to detect myocardial ischemia; the concomitant use of ultrasound contrast agents may demonstrate myocardial perfusion and enhance the detection of regional wall motion abnormalities.(51) Almeida *et al.* demonstrated abnormal myocardial perfusion reserve in 2 of 25 stable patients with SCD, subsequently confirmed

with single photon emission computed tomography (SPECT).(52) Limited use of this modality reflects technical challenges, operator skill variability and lack of standardized perfusion protocols.(53)

Nuclear Scintigraphy

Norris *et al.* performed resting thallium imaging in 10 patients with SCD during pain crisis. Four patients were found to have defects, though only two had cardiac enzyme elevation suggesting hypoperfused but noninfarcted myocardium.(29) Maunoury *et al.* assessed myocardial perfusion in 23 patients known to have SCD using treadmill and/or dipyridamole stress thallium-201 SPECT imaging. Among these 4 had cardiac symptoms (2 angina, 2 heart failure), 10 had atypical chest pain and 9 were asymptomatic. 61% of 23 patients had abnormal scan with reversible defects noted in 9 and fixed defects seen in 5 patients. The 4 patients with cardiac symptoms had abnormal perfusion; with subsequent coronary angiography in all 4 revealing no epicardial coronary obstruction.(27) De Montalambert *et al.* performed a similar study in 22 individuals with sickle cell homozygous gene expression, and found reversible perfusion abnormalities in 64%. Those with abnormal myocardial perfusion were older, had lower hemoglobin levels and had experienced more frequent vaso-occlusive crises.(23)

Cardiac Magnetic Resonance

Recognizing that microvascular disease is a more likely mechanism for myocardial injury in SCD, the limited spatial resolution of nuclear imaging (~1 cm) may not be the ideal technique to identify myocardial ischemia that is non-transmural or limited to the subendocardium. The 2–3 mm spatial resolution of myocardial perfusion imaging with cardiac magnetic resonance (CMR) (54) is ideally suited to identify microvascular abnormalities. This was demonstrated by Panting *et al.* in patients with cardiac syndrome X, a condition where metabolic abnormalities produce typical angina in the absence of epicardial coronary stenosis. Using adenosine vasodilator stress, quantitative subendocardial perfusion abnormalities and reproduction of symptoms occurred in patients but not in healthy controls.(55) Our group applied the same protocol in an ambulatory setting and identified a cohort of individuals affected by SCD with subendocardial ischemia and no epicardial coronary disease.(56)

CMR is also unique in its ability to quantify myocardial iron overload, an important consideration in light of these patients' transfusion requirements. The effect of iron aggregates on magnetic relaxation of protons can be quantified using T2 star (T2*)-based techniques.(57) Wood *et al.* studied 17 patients with transfusion-dependent SCD, and found no myocardial iron overload in these patients.(58) We similarly found normal myocardial T2* in patients diagnosed with SCD despite microvascular abnormalities, suggesting that ischemic heart disease is not a result of myocardial iron overload.(56)

Subsequent case reports have demonstrated the utility of CMR in identifying myocardial infarct scar in a similar group. Cine imaging enables the measurement of myocardial wall thickness and evaluation of global and regional cardiac function. Late gadolinium enhancement (LGE) is a technique whereby regions of disrupted myocyte membrane integrity and interstitial expansion accumulate extracellular gadolinium-based contrast 5–10 minutes after intravenous administration unlike complete clearance from regions of uninjured myocardium.(59) These areas of contrast accumulation appear bright on T1-weighted imaging making it possible to visualize infarcted myocardium (Figs. 3–4). Pavlu *et al.* described a 50 year-old female with history of sickle cell disease who had chest pain unlike prior sickle cell crises and had elevated troponin levels. While cardiac catheterization

demonstrated angiographically-normal coronary arteries, LGE demonstrated subendocardial hyperenhancement of infarct scar.(4)

MANAGEMENT

The usual management strategies for crisis such as supportive care(21) and red cell exchange transfusion(4, 22, 32) do not typically include established therapies for acute ischemic syndromes due to coronary artery disease(60, 61) such as heparin(4, 24, 31) aspirin(4, 31, 32) -blockade(24, 31), clopidogrel(4), angiotensin-converting enzyme inhibitors(24) and nitroglycerin(32). Red cell transfusions to lower HbS are well-established in addressing vaso-occlusive ischemic injury in the brain.(62) Khalique and colleagues recently described applying the same approach to treat myocardial injury(63); keeping HbS<30% was associated with absence of recurrent MI during 34-month follow-up. Before these approaches can be routinely advocated for individuals with SCD identified to have ischemic heart disease, prospective clinical trials are needed with endpoints that ideally include measures of irreversible injury and myocardial salvage.

There has been considerable debate regarding the role of nitric oxide (NO) as a therapeutic agent in vaso-occlusive sickle cell crisis. Although small studies have suggested that NO therapy reduces time to resolution of crisis episodes(64–66), a larger prospective trial showed no such reduction when NO was used to treat vaso-occlusive crisis.(67) In a mouse coronary ligation model of injury and reperfusion, Hataishi *et al* demonstrated that inhaled NO given before reperfusion was beneficial in reducing subsequent extent of myocardial injury.(68) Given the mechanistic appeal of NO in SCD, it may warrant further evaluation as a myocardial protective agent in sickle cell-related myocardial infarction.

Implantable cardioverter-defibrillators (ICDs) have significantly reduced mortality due to sudden cardiac death in patients with both ischemic and non- ischemic cardiomyopathy with reduced systolic function.(69) Such devices are typically deployed to recognize and treat ventricular arrhythmias, whose frequency increases in the face of myocardial scar. While specific studies evaluating ICD utility in patients with SCD have not been published, their potential to deliver life-saving therapy in patients has been consistently demonstrated in other populations with significant left ventricular systolic dysfunction due to a variety of causes suggesting that the high-risk patient with SCD may benefit as well.

UNKNOWN AND TRANSLATIONAL CONSIDERATIONS

Much remains to be defined in understanding myocardial ischemia and infarction in sickle cell disease. MI does appear to be present in patients with sickle cell disease, but the exact incidence remains unknown. It is also unknown how often subclinical myocardial ischemia occurs in stable patients with SCD, or what the prevalence is in this group presenting with chest pain. Routine evaluation for myocardial ischemia is uncommon, as young patients with SCD do not fit the stereotypical profile of the older patient with atherosclerotic risk factors presenting with chest pain where myocardial ischemia is immediately suspected.

Further investigations defining the prevalence of myocardial ischemia in patients with SCD presenting with acute chest pain are necessary. Until such data is available, we suggest careful monitoring of the patients who presents with crisis. It is prudent to obtain serial electrocardiograms and measure cardiac biomarkers such as troponin-I in patients with underlying SCD who present with chest pain without a clear diagnosis of pulmonary infection or other noncardiac etiology. Dynamic ECG changes or abnormalities of biomarker measurement should prompt further evaluation. As microvascular disease may contribute to ischemia and injury, CMR may be advantageous in making the correct diagnosis given the lack of ionizing radiation in this often young population and ability to

demonstrate both microvascular disease as well as infarcted myocardium with a resolution not matched by other modalities.

While suitable animal models of SCD exist(70), no studies to date have investigated myocardial ischemia and injury in these models. It is encouraging to note, however, the potential vascular benefit of novel therapeutics developed through careful preclinical investigations(71). Given the unique ability of CMR to precisely quantify the presence and extent of myocardial ischemia, edema, injury and microvascular obstruction in both animals as well as in human subjects, this imaging modality would seem the ideal choice for future translational and clinical studies aimed at improving diagnosis, treatment and outcomes.

This work has provided a detailed summary of microvascular occlusion mechanisms (Figure 1) that may be responsible for the underrecognized clinical manifestations of ischemic heart disease in SCD. Recognizing both mechanisms and potentially deadly clinical events behooves new, interdisciplinary programs of translational research to better prevent, detect and treat myocardial infarction in SCD. Such programs must include investigators with established understanding of SCD pathophysiology as well as clinicians and scientists adept in ischemic heart disease, with both parties open to filling gaps in knowledge laid bare when approaching the unmet needs of this population. Agencies such as the new National Center for Advancing Translational Sciences should support such interdisciplinary research programs, particularly through funding mechanisms that encourage critical examination of potentially incorrect assumptions about ischemic heart disease in SCD.

CONCLUSIONS

In summary, increasing histopathological, serological and imaging data indicate the presence of myocardial infarction in SCD is likely mediated by microvascular disease rather than epicardial coronary disease. In light of this accruing evidence, myocardial infarction should be a consideration in the individual with sickle cell disease with chest pain. The paucity of data regarding management strategies for MI in SCD underscores the need for clinical trials that explore therapeutic options to reduce morbidity and mortality. In light of the high risk of sudden death in this vulnerable cohort, clinicians should consider risk assessment tools to identify those who are at higher risk for adverse cardiac outcomes.

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Figure 1.

Mechanism of microvascular occlusion in sickle cell disease

Polymerization of HbS alters cell structure integrity resulting in an irreversible sickle cell (ISC). Accumulation in areas of vessel narrowing is compounded by increased expression of cell adhesion molecules (CAM). Cell membrane disruption exposes phosphatidyl serine moieties that incite inflammatory responses and activation of tissue factor favoring a hypercoagulable state. Free hemoglobin from hemolysis follows sets in motion a cascade of events including nitric oxide (NO) scavenging, formation of free radicals and endothelial cell activation. Increased viscosity with reduced NO bioavailability results in microvascular obstruction.

Figure 2.

Histopathologic findings at autopsy of microvascular obstruction and myocardial infarction are shown from a 35 year-old male with SCD who was found dead at home.

Echocardiography 2 months prior to death reported normal LV size and EF 55%, estimated right ventricular systolic pressure 20 mmHg. Epicardial coronaries were free of obstructive disease, and there was no pulmonary embolism. Sickle cells are seen causing microvascular obstruction of an arteriole (A, black arrow). Myocardium shows multiple regions of contraction band necrosis consistent with recent myocardial infarction (B, dotted circles) along with regions of interstitial fibrosis (C, blue arrow).

Figure 3.

Diagnosis of myocardial infarction in SCD may be delayed. Electrocardiography (left panel) in a 37 year-old patient with SCD presenting to the ED with chest pain showed left ventricular hypertrophy with repolarization abnormalities and ventricular ectopy; cardiac biomarkers were not drawn. Echo indicated moderate LV dysfunction, with estimated ejection fraction of 35% and segmental wall motion abnormalities. Cardiac magnetic resonance was performed 5 days after admission; late post-gadolinium enhancement imaging (right panel) indicated inferior wall injury with regions of microvascular obstruction (arrowheads) within areas of hyperenhancement (arrow) i.e. injured myocardium. Review of the initial ECG after recognition of MI by CMR revealed injury current (ST elevation) in the inferior leads, notably III and aVF. Cardiac computed tomography (not shown) indicated zero calcium and angiographically-normal coronary arteries. LA = left atrium, LV = left ventricle.

Figure 4.

A 34 year-old male with SCD on long-term hydroxyurea with a history of TIA presented to the ED with chest pain. ST elevation was identified on the ECG (A), prompting invasive angiography 2 hours after presentation that showed angiographically-normal coronary arteries (B, C). CMR with late gadolinium enhancement imaging (D, E) showed transmurular scar (blue arrows) plus regions of microvascular obstruction (red arrows). Antiplatelet therapy and exchange transfusion were initiated with discharge HbS of 26.9%.

Table 1**Published Cases of Myocardial Infarction in Patients with Sickle Cell Disease**

Reference	Study type	N	Number with MI	Diagnostic findings
Assanasen, 2003(20)	Case report	1	1	ECG changes, cardiac enzymes, autopsy
Maunoury, 2003(27)	Case series	23	5	ECG changes (8 patients only), fixed defect on thallium SPECT
de Montalembert, 2004(23)	Case series	22	5	ECG changes (3 patients only), fixed defect on thallium SPECT
Pavlu, 2007(4)	Case report	1	1	ECG changes, cardiac enzymes, infarct scar by CMR
Dang, 2005(22)	Case report	3	3	ECG changes, cardiac enzymes
Sherman, 2004(31)	Case report	1	1	ECG changes, cardiac enzymes
Wang, 2004(32)	Case report	1	1	ECG changes, cardiac enzymes
Deymann, 2003(24)	Case report	1	1	ECG changes, cardiac enzymes
Martin, 1996(26)	Chart review	72	7	ECG changes (2 patients only), autopsy
Norris, 1991(29)	Case series	19	4	ECG changes, cardiac enzymes (2 patients only), fixed defect on thallium SPECT
Saad, 1990(30)	Case report	1	1	ECG changes
McCormick, 1988(28)	Case report	1	1	ECG changes, autopsy
Martin, 1983(25)	Case report	1	1	ECG changes, autopsy
Barrett, 1984(21)	Case report	2	2	ECG changes, autopsy
Woodruff, 1970(72)	Case report	1	1	ECG details unavailable
Rubler, 1967(73)	Case report	1	1	ECG details unavailable, autopsy
Uzsoy, 1964(74)	Chart review	9	1	ECG details unavailable, autopsy
Tanner 2006(75)	Case report	1	1	Infarct scar by CMR
Oliveira, 1963(33)	Case report	1	1	ECG changes, autopsy

ECG = electrocardiography; SPECT = single photon emission computed tomography; CMR = cardiac magnetic resonance

'cardiac enzymes' indicates abnormal values of various biomarkers such as MB fraction of creatinine kinase, troponin-I and troponin-T