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[Review article]

A proposed role for sepsis in the pathogenesis of myocardial calcification

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INTRODUCTION

Myocardial calcification is a rare and life-threatening condition that is a recognised complication of ischaemic heart disease, cardiac surgery, rheumatic fever and myocarditis. It is distinct from coronary artery or valvular calcification, and can be seen in patients with abnormal calcium metabolism[1]. Its presence in the context of sepsis is less well recognised and the mechanisms responsible are poorly understood. We review the relevant literature and propose a mechanistic theory for its pathogenesis.

SUBJECTS AND METHODS

The objective of this paper is to summarize the available evidence for the development of myocardial calcification during sepsis and provide a possible mechanism. In particular: (a) we attempt to highlight the clinical course of these patients; (b) evaluate the investigations carried out in the cases reviewed; (c) analyse the histological findings; and (d) describe the features of neonatal cases in comparison with adults. A literature search was performed using PubMed, Embase and Medline using combinations of the terms 'myocardial calcification' and 'sepsis' or 'sirs' or 'systemic inflammatory response syndrome' with the limitations 'humans' and 'English language'. We identified and assessed a total of 11 case studies reporting on myocardial calcification in septic patients (table 1) in order to better understand the clinical course, disease trends and proposed mechanisms regarding this condition.

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RESULTS

Clinical course

All cases described critically unwell patients who required ICU admission. Seven received catecholamine therapy and two required renal replacement therapy. There was little information regarding pre-morbid status or past medical history. However, three patients had haematological malignancy: one with a previous diagnosis of leukaemia and one who presented with neutropenic sepsis while on chemotherapy for leukaemia. The other was diagnosed with hairy cell leukaemia during admission.

One patient survived, seven died and one study did not report the final outcome. Interestingly, five of nine papers described a secondary deterioration of the patient

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Table 1 Case studies of myocardial calcification in sepsis

Authors, country, (year)	Age	Sex	Presentation	Catecholamines	Renal replacement	Cardiac enzymes	Echocardiogram	CT	Histology	Outcome
Barson et al., USA (1981) 8	< 1	–	Shock	–	–	–	–	Myocardial calcification	–	Survived
Itoh et al., Japan (1997) 10	47	F	Sepsis	Yes	–	High	Oedematous thickening of ventricular wall and hypokinesia	–	Necrosis with lymphocytic infiltration and heavy calcium deposits in areas of inflammation	Died day 17
Lapatto-Reiniluoto et al., Finland (2000) 3	34	M	Cellulitis	Yes	Yes	High	Increased echodensity of LV and EF 30%	LV myocardial calcification	Calcification in the myocardium surrounding the entire left ventricle	Died day 50
Schellhammer et al., Germany (2002) 30	20	F	Sepsis	Yes	–	–	Myocardial calcification	Diffuse LV calcification	–	–
Rossi and Santos, Brasil (2003) 2	27	M	Pneumonia	Yes	–	–	Normal	–	Widespread interstitial fibrosis, foci of myocytolytic myocytes and calcified myocardial cells associated with inflammatory cells	Died day 27
Sinicina et al., Germany (2005) 4	33	M	Sepsis	Yes	–	High	Increased density of septal myocardium (LVF not mentioned)	–	Widespread intra- and extracellular calcium deposits; calcified myocardiocytes; interstitial fibrosis; myocytolytic myocytes with inflammatory cells	Died day 28
Simonson et al., USA (2007) 36	58	M	Neutropenic sepsis & leukaemia	Yes		High	Global LV systolic dysfunction with EF 20%	High attenuation of LV myocardium	–	Survived
Al Senaidi et al., Canada (2009) 9	< 1	–	Cardiogenic shock	–	–	–	Diffuse hyperechogenic foci	–	Myofibre necrosis and calcifications surrounded by lymphocytic infiltrates	Survived
van Kruijsdijk et al., The Netherlands (2011) 5	56	M	Diarrhoea & leukaemia	–	–	High	Pronounced echodensity of LV myocardium and LV dysfunction	LV myocardial calcification	–	–
Austin et al., USA (2012) 37	44	M	Renal failure & liver failure	–	Yes	–	Diffuse acoustic shadowing throughout LV with preserved LVF (EF 71%)	Increased LV myocardial attenuation	Diffuse myocardial calcification throughout LV	Died day 33
Akbas et al., Turkey (2014) 38	36	F	Sepsis & leukaemia	Yes	No	High	Hypokinetic LV with EF 40%	Diffuse LV calcification	–	Died day 37

LV: left ventricular; EF: ejection fraction; LVF: left ventricular function; ND: not declared; CT: computed tomography.

prior to the myocardial calcification being discovered. One patient was discharged from the ICU and died suddenly two days later. The diagnosis of myocardial calcification was made at post-mortem[2]. Three others developed acute heart failure after initial improvement[3-5] and another developed haemodynamic collapse and cardiomegaly on post-mortem examination[6]. The surviving patient did not have this pattern of secondary deterioration.

Investigations

Serum calcium or phosphate levels were high in only two cases. Cardiac enzymes were elevated in six patients and abnormal electrocardiograms were reported in four of the studies with no unifying pattern between them. Six papers described computerised tomography scans reporting myocardial calcification and five studies described echocardiogram findings consistent with calcification of the myocardium (e.g. increased echodensity of the myocardium or increased acoustic shadowing) with hypokinesia and varying ejection fractions. The only reported normal echocardiogram was of the patient who died suddenly after being discharged from ICU[2]. There is inadequate evidence to clarify whether these imaging methods can offer any predictive value in assessing patient mortality in patients with myocardial calcification. Echocardiography offers a versatile, bedside and cost-effective early diagnosis although its specificity remains low. Conversely, CT offers high precision patterns of calcium deposition (localised versus extensive) that offer a higher yield of differentiability in diagnosis[7].

Histological findings

Post-mortem was performed in five cases and detailed histology of the heart given in two papers which reported similar histological findings including: perimysial interstitial fibrosis, myocytolytic myocytes with necrosis, foci of calcification and inflammatory cell infiltrate. Inflammatory cells were found in areas of calcification[2,4]. These findings were not considered consistent with infectious myocarditis, viral myocarditis or idiopathic myocarditis.

Rossi and Santos used their histological findings to suggest a two-stage process in which an initial insult caused focal myocytolytic necrosis followed by heavy calcium deposition within the necrotised cardiomyocytes[2]. The nature of the insult causing necrosis was considered secondary to sepsis-related disturbances in microvascular flow through the myocardium. This in turn would result in an ischaemic insult and inflammation which primed areas for dystrophic calcification. Increased expression of inducible nitric oxide synthase (iNOS) was found within cardiomyocytes, implicating high levels of nitrous oxide as a potentially significant factor in cell injury and calcification[2].

Neonatal cases

Two neonatal cases of myocardial calcification occurred in the context of coxsackie B viral infection. Both neonates were febrile an in cardiogenic shock. One improved with supportive treatment[8]. The other required heart transplantation. Histological analysis of the explanted heart confirmed myocardial calcifications[9], whereas chest radiographs made the diagnosis in the other case. The lymphocytic infiltrates described in the explanted heart were in keeping with a viral-induced myocarditis, and are different from the inflammatory changes reported in the adult hearts which have a more unique histology[2]. Given the different clinical picture of the adult cases (severe sepsis followed by secondary cardiovascular collapse) and the difference in histology, it seems that the neonatal cases represent calcification secondary to viral myocarditis, a different entity to that described in the adult cases and one more recognised than sepsis-related myocardial calcification[1]. One adult case reported predominantly lymphocytic infiltrates on histology, consistent with viral myocarditis and high virus neutralising antibody to coxsackie A, although the authors note that this does not confidently establish a diagnosis of viral myocarditis[10].

DISCUSSION

As myocardial calcification in sepsis is a rare entity, its exact mechanistic characteristics remain to be elucidated in more depth. Preliminary hypotheses are aimed at structuring our understanding of this condition. These have drawn on understanding of myocardial calcification not associated with sepsis, and the theories of sepsis-related myocardial dysfunction and injury. We propose a mechanism by which a severe septic insult induces inflammatory and oxidative stress-related damage to cardiomyocytes which provide a site for dystrophic calcification to take place (figure 1).

Dystrophic and metastatic calcification

Myocardial calcification is described as dystrophic when it occurs in areas of damaged myocardium in a patient with normal calcium homeostasis (e.g. myocardial infarction) and as metastatic when it occurs in viable myocardium in the context of abnormal calcium homeostasis, most commonly in chronic renal failure patients with secondary hyperparathyroidism[11] and haemodialysis patients[12]. Given that calcium balance was

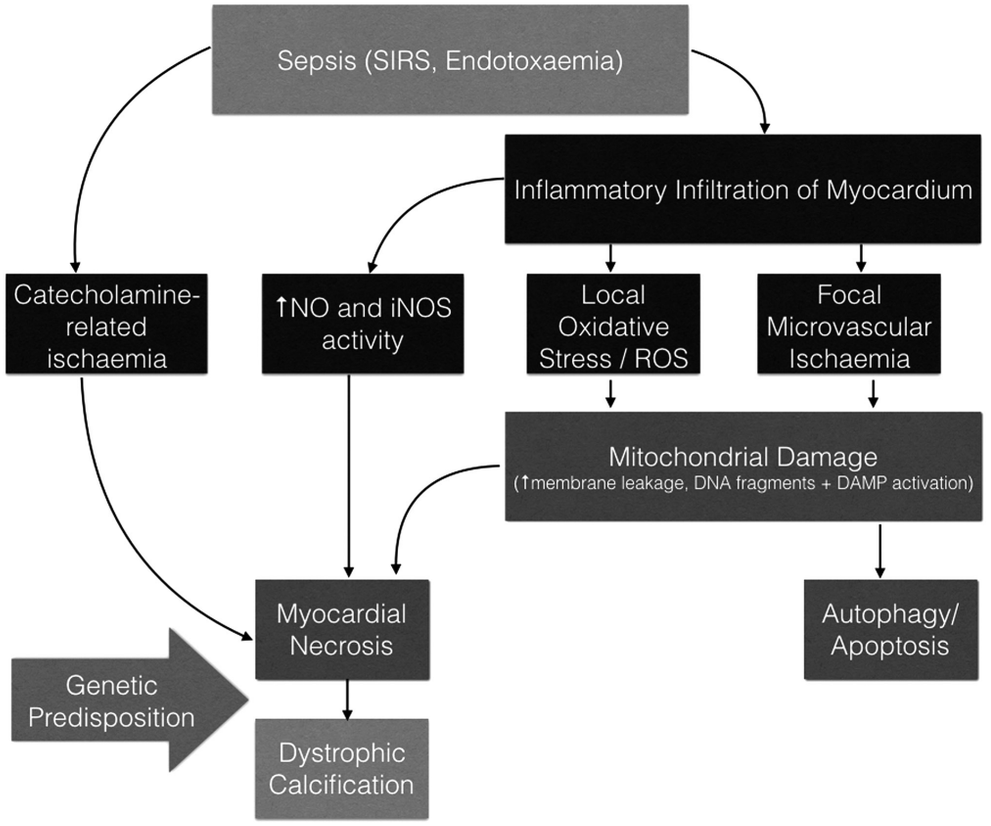

Fig. 1 Proposed mechanism.

rarely deranged in these cases, and that the calcification seems to take place in inflamed or necrotised myocardium, dystrophic calcification seems a more fitting description. However, the clinical course and histology in these cases point away from classic infected myocarditis[2]. Furthermore, describing the calcification as dystrophic does not help us elucidate the mechanism of injury to the myocardium which primed it for calcification.

Myocardial dysfunction and myocardial damage

Sepsis-related myocardial injury is a complex process. Myocardial dysfunction occurs within 24 hours of sepsis and manifests as left ventricular dysfunction, often with reduced ejection fraction, and usually reverses within 7-10 days[13,14]. It is frequently associated with elevated cardiac enzyme levels[15]. The mechanisms of myocardial dysfunction are thought to be a consequence of the profound inflammatory response seen in sepsis rather than a reaction to the pathogenic organism or endotoxins[16], although there is some evidence for cardiomyocytes internalising endotoxins which go onto directly impair their function[17].

Global ischaemia during sepsis has been largely refuted as a mechanism of myocardial injury[18]. However, heterogeneous microvascular blood flow, in which focal areas of myocardium are subject to ischaemic insult through poor microvascular flow, impaired oxygen extraction and aerobic metabolism, has been proposed[16,19]. A multitude of inflammatory mediators, such as TNF-alpha, IL-1beta and IL-6, have also been shown to depress myocardial function and reduce contractility[13]. Intracellular changes induced by the inflammatory mediators and associated with depressed myocardial activity include reduced calcium exchange within cells, reduced sensitivity of myofibrils to calcium, increased nitrous oxide production, and mitochondrial dysfunction. All have all been observed in experimental models of sepsis[16].

Reversibility is an important feature of sepsis-related myocardial dysfunction and it would seem cell necrosis is rare[20], suggesting that the SIRS of sepsis does not cause lasting to damage to the heart. Myocardial depression may even be a 'survival mechanism' during a time of metabolic stress[21]. Increased cardiac enzymes in severe sepsis suggests myocardial necrosis but a review of the literature on structural changes to the human heart during sepsis concluded that, although inflammatory changes within cardiomyocytes was common, cell necrosis was rare and likely of little importance[22].

However, in a small percentage of fatal cases sepsis-related, there is evidence of a correlation between infection and cardiomyocyte necrosis[23]. Prolonged cases of sepsis have been shown to have a more intense inflammatory

change in the myocardium. Inflammatory cell infiltrate, focal myofibril disruption, TNF-alpha expression and iNOS expression were greater in the hearts from cases of prolonged sepsis than controls (the study looked at hearts from patients dying from acute pancreatitis)[24]. No necrosis or calcification was reported. Animal studies have more readily found histological evidence of inflammatory-mediated myocardial damage and necrosis[22]. Wong et al. found foci of aseptic myocardial necrosis and intense myocardial inflammation in the right ventricle of rats after injection of E. coli lipopolysaccharide[18]. The histological findings in their so-called endotoxin-induced myocarditis were felt to be distinct from myocarditis caused by direct infection of the myocardium (i.e. infectious myocarditis). A wide range of inflammatory mediators and pathways were implicated. Again, no calcification was reported.

Mitochondrial dysfunction and injury

The process by which sepsis may initiate myocardial damage is not clear but one possible mechanism is mitochondrial dysfunction. Indeed the mitochondria of myocardial fibres have long been implicated as the initial focus of myocardial calcification associated with cardiac surgery and advanced renal disease[11]. Myocardial mitochondrial injury during sepsis is thought to be a consequence of inflammatory infiltration. The inflammation causes cellular oedema, which impairs microvascular flow and may generate cytopathic hypoxia, and increased reactive oxygen species production[22]. This ischaemia and oxidative stress disrupts the mitochondrial membrane and damages other mitochondrial structures[25]. Fragments of mitochondrial DNA leak into the cytosol where they act as danger-associated molecular patterns (DAMPs) and instigate further inflammatory response within the cardiomyocytes[26]. This triggers apoptotic and autophagic pathways[22] which may cause lasting structural damage given cardiomyocytes poor ability to regenerate[18]. Although necrosis seems to be uncommon, the histological findings of intense inflammatory infiltrates associated with necrosis in sepsis-related myocardial calcification suggest necrosis is a potential outcome of myocardial inflammation and mitochondrial damage.

Nitrous oxide and myocardial injury

The high levels of inducible nitrous oxide synthase (iNOS) observed in Rossi's and Santos' case of myocardial calcification in sepsis lead them to propose a role for nitrous oxide (NO) in initiating myocardial injury. Wong et al. also found increased expression of nitrous oxide synthase-2 in their animal model of endotoxin-induced myocarditis[18]. High levels of NO are seen in sepsis and are known to induce cytotoxic processes and cell death[27,28]. NO may be elevated in a number of other physiologic and pathological states but the intensity of iNOS expression in the septic human heart was not found to a similar degree in post-mortem studies of dilated and ischaemic cardiomyopathy hearts, suggesting it a finding unique to the septic state[29].

Catecholamine-related myocardial injury

Another possible contributory factor to the myocardial injury in septic patients is the prolonged use of catecholamines. This mechanism was proposed in two case reports[3,30] as adrenergic overstimulation is known to cause myocardial ischaemia and necrosis[31]. A study of 122 patients who received catecholamines found that 17.5% had evidence of myocardial cell damage, defined as a troponin rise of greater than 25% of the admission level[32]. The extent to which troponin elevation reflects myocardial necrosis in human hearts has not been established[33]. Although troponin rise is associated with increased mortality, it may be seen in reversible sepsis-related myocardial dysfunction.

Functional impact of calcification

The effect of myocardial calcification on cardiac function is not clear[1] and the possibility of it existing at a subclinical level in some septic patients, therefore being more common than the literature suggests, cannot be ruled out. However, case reports of myocardial calcification in non-septic patients tend to have a diagnosis made at post-mortem in patients who presented with intractable heart failure[34], although Ito et al. report on a case of apical myocardial calcification in a stable patient[1]. Intuitively the damaged myofibrils and widespread calcification must have contributed to cardiac failure. The myocardial dysfunction of the strong inflammatory response evidenced at histology is also likely to have significant functional impact.

Genetic factors

The reason these few patients developed myocardial damage during sepsis and went on to develop calcification is unknown. Rossi and Santos proposed the possibility of a genetic disposition towards calcification after a study in mice found a locus on chromosome 7 which pre-disposed to calcification of necrotised cells[2,35]. Genetic abnormality would perhaps explain the scarcity of sepsis-related myocardial calcification, and would support a theoretical two-hit model: a genetic predisposition to calcification combined with a septic insult severe enough to induce significant myocardial necrosis.

CONCLUSION

Sepsis-related myocardial calcification is a rare and life-threatening complication of severely septic patients. The clinical course and post-mortem histology suggests it is the consequence of inflammatory-mediated myocardial necrosis, with dystrophic calcium deposition in areas of necrosed myocardium. The necrotic myocardium identified on histology does not directly correspond with the theories of the reversible myocardial dysfunction seen in sepsis, and suggests that particularly severe sepsis has the potential to inflict lasting structural damage to the heart. Foci of impaired microvascular flow and oxygen delivery, as well as catecholamine-related injury, may also contribute to myocardial damage. Mitochondrial damage due to increased oxidative stress may be the initial source of cellular injury. Genetic factors are also likely to have a contextual role in the genesis of this disorder. Sepsis-related myocardial calcification seems to carry a high mortality, and in five of the nine cases reviewed was associated with a secondary deterioration in patients who had responded positively to initial treatment. Future steps include more robust molecular analyses of myocardial samples from patients with this sepsis-related calcification in addition to the application of more targeted cardiac supportive interventions. The development of an international registry may be one route by which to coordinate research and treatment efforts. Treatment options remain supportive in the current era, although there may be a role for heart transplantation. Awareness of this rare complication in patients with long-term sepsis and secondary deterioration suggests a role for earlier recognition and supportive measures in the management of this life-threating disorder.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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