

# Septic cardiomyopathy: pathophysiology and prognosis

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## ABSTRACT

Septic cardiomyopathy is a separate clinical entity clearly distinct from myocarditis on histological grounds. Physiologically it characteristically presents, unlike other types of heart failure, with normal or increased cardiac output with normal or low preload pressures & a reduced systemic vascular resistance. Speckle tracking echocardiography is now the diagnostic tool of choice for detecting subtle changes in myocardial dysfunction

Ventricular contractility is invariably reduced to some degree in septic shock but, if severe ventricular dysfunction with low blood pressure and a falling cardiac output develops, mortality is twice that of septic shock without cardiac organ failure. However if the patient survives the episode of sepsis, septic cardiomyopathy is largely reversible since the changes are predominantly functional rather than structural although it is as yet uncertain if this applies when contraction band necrosis has developed as a result of the use of high doses of vasopressors.

**Key words:** Sepsis, septic shock, septic cardiomyopathy, sepsis induced cardiomyopathy, ventricular contractility, speckle tracking echocardiography, ventricular re-synchronisation.

## INTRODUCTION

In 1981 Calvin et al (1) reported myocardial dysfunction, defined as reduced ejection fraction and increased end-diastolic volume index, in septic patients who had been volume resuscitated. A few years later in a study using pulmonary artery catheters and radionuclide imaging, Parker et al (2) described septic cardiomyopathy (SC) or

sepsis-induced cardiomyopathy (SICM) as a distinct cardiomyopathy in patients with septic shock characterised by a high cardiac output, low systemic vascular resistance (SVR) and maintained stroke volume provided the patient was adequately volume resuscitated. This study also reported somewhat surprisingly that survivors of septic shock had increased left ventricular (LV) end-diastolic volumes and reduced ejection fraction (<0.4) whereas non-survivors had higher ejection fractions and normal ventricular volumes. Furthermore they discovered that the survivors had no permanent structural damage when reassessed after recovery. Although sepsis was first described more than 2000 years ago (3) there is still disagreement about aspects of diagnosis & prognosis of specific organ failures and this has remained the case for SC since it was first described over 30 years ago.

This article reviews the definition, aetiology, pathology, diagnosis and prognosis of septic cardiomyopathy.

## DEFINITION

It is possibly not surprising that it has proved difficult to define a condition that is caused by a syndrome and not a fundamental pathology. Sepsis and septic shock are caused by

multiple primary pathologies (pneumonia, UTI, peritonitis, meningitis etc) which have individual signatures with regard to bacterial toxins released, cytokine expression, the impact on individual organs and the time course of these events. In addition septic cardiomyopathy may develop in a patient with pre-existing cardiac disease & this will modify the patho-physiological picture that results.

Since the heart is inextricably linked to the

wider circulation, assessment of ventricular function depends on the preload, determined by the intravascular volume status and the venous compliance and the afterload determined by the systemic arteriolar 'tone'. The move towards non-invasive assessment of cardiac function, in particular conventional echocardiography and away from the traditional invasive approaches such as pulmonary artery catheterisation, which provided quantitative information on left ventricular (LV) preload and right ventricular (RV) afterload, explains some of the conflicting results reported regarding changes in ejection fraction and ventricular volumes associated with SC. The typical picture seen in SC is ventricular dilatation, reduced ejection fraction, reduced ventricular contractility and both right and left ventricular systolic and diastolic dysfunction with a reduced response to volume infusion. (4) However as shown in Table 1, compared to a normal subject, four hypothetical patients with haemodynamic profiles compatible with sepsis may all have the same stroke volume but significantly impaired left ventricular stroke work indices (LVSWI) which better reflects ventricular contractility and is a better, albeit more invasive, method for defining myocardial dysfunction in sepsis than changes in ejection fraction and ventricular volumes. Even in early sepsis there may be some degree of ventricular dysfunction but this could be too subtle to be detected by conventional non-invasive techniques and can only be detected by recently described and more sophisticated echocardiographic techniques such as 'speckle tracking'.

## AETIOLOGY

The possible causes of septic cardiomyopa-

Table 1. Comparison of left ventricular end diastolic volume (LVEDV), ejection fraction (LVEF), Stroke volume (SV), systemic vascular resistance (SVR) and left ventricular stroke work in a normal subject with HR 70/min; MAP 90mmHg; CVP +6mmHg; LAP +10mmHg (from mid axillary line) & patients a) to d) at different stages in sepsis assuming HR 90/min; MAP 60mmHg; CVP +10mmHg; LAP +15mmHg; BSA 1.7m<sup>2</sup>

Patient	LVEDV mls	LVEF %	SV ml	Cardiac index l/min/m <sup>2</sup>	SVR dyn.sec.cm <sup>-5</sup>	LVSWI gm/m <sup>2</sup>
Normal MAP 90; CVP 6 LAP 10 HR 70	120	60	72	2.9	1340	46
a)	75	60	45	2.4	980	18
b)	100	60	60	3.2	740	22
c)	120	60	72	3.8	620	26
d)	150	60	90	4.8	490	32

BSA, body surface area  
CVP, ventral venous pressure  
HR, heart rate  
LAP, left atrial pressure  
LVEDV, left ventricular end diastolic volume  
LVEF, left ventricular ejection fraction  
LVSWI, left ventricular stroke work index  
MAP, mean arterial pressure  
SV, stroke volume  
SVR, systemic vascular resistance

thy (SC) are listed in Table 2. Cunnion et al. investigated the possibility of reduced coronary artery flow as a cause of SC by performing coronary sinus catheterisation in a group of patients with septic shock but found that coronary flow was the same or greater than in normal controls. (5) This effectively rules out global ischaemia as a cause of myocardial depression in sepsis other than possibly in patients with pre-existing significant coronary artery disease. However the coronary microcirculation is definitely abnormal in

sepsis with major re-distribution of flow, 'shunting', endothelial disruption and fibrin deposition. (6) Myocardial depressant factor includes a variety of molecules all with depressant effects on the myocardium not only bacterial derived toxins such as endotoxin / lipopolysaccharide but also TNF- $\alpha$  and IL-1 $\beta$ . (7, 8) Sepsis leads to the expression of inducible NO synthase (iNOS) in the myocardium which results in high levels of nitric oxide locally. This disrupts intracellular calcium metabolism, reducing cytosolic calcium levels and im-

pairing contractility. It also affects mitochondrial function by reducing the activity of complexes I & II of the mitochondrial respiratory chain. It has been suggested that this may represent a protective response similar to the hibernating myocardium seen in ischaemia-reperfusion injury but the high mortality associated with this condition suggests otherwise. Apart from global coronary ischaemia it would appear that all the other causes listed in Table 2 contribute to some extent to myocardial dysfunction seen in sepsis.

Table 2.

**Possible causes of the cardiomyopathy in sepsis**

Global ischaemia

Micro-circulatory ischaemia

Bacterial toxins: lipopolysaccharide (LPS) or endotoxin & other 'myocardial depressant factors

Cytokines: TNF- $\alpha$ , IL-1 $\beta$ ,

Nitric oxide

Damage associated molecular patterns (DAMPs): histones & HMGB1

Direct mitochondrial dysfunction

High doses of  $\beta$ -agonist vasopressors

DAMPs, damage associated molecular patterns  
IL-1 $\beta$ , interleukin 1 $\beta$   
LPS, lipopolysaccharide  
TNF- $\alpha$ , tumor necrosis factor  $\alpha$

## **PATHOLOGY**

Cardiac histology in patients with SC typically shows significant interstitial oedema with large numbers of white blood cells (neutrophils and macrophages) in the interstitium but no evidence of myofibril destruction such as seen in viral myocarditis. (8) Such changes are likely to be totally reversible if the patient survives the episode of sepsis. However, in patients on high doses of vasopressors, disruption of actin-myosin linkage may occur leading to so called 'contraction band necrosis'. Should such a patient survive then this may represent a structural and irreversible change.

At a microcirculatory level blood flow is reduced and re-distributed with 'shunting' which leads to localised areas of ischaemia and in the capillary lumen there is margination of neutrophils, platelet aggregation and fibrin deposition and increased endothelial permeability causing interstitial oedema. At a cellular level tissue oxygen uptake and utilisation is reduced due to the disruption of the mitochondrial respiratory chain by the increased levels of local nitric oxide produced as a result of increased expression of iNOS. The excess production of NO leads to increased local levels of peroxynitrite which result in long-term myocardial depression. (9)

## **PHYSIOLOGY**

The typical circulatory pattern associated with sepsis is a tachycardia, unless on  $\beta$ -blockers, initially normal or reduced LV preload pressures & a normal or increased cardiac index when adequately volume resuscitated due to a reduced SVR. However as shown in Table 1 the ventricular contractility (LVSWI) is nonetheless reduced. Ognibene et al. using a PA catheter and cineangiography confirmed that patients with sepsis and septic shock had reduced left ventricular contractility as assessed by LVSWI and also demonstrated that in these patients the response to volume loading was significantly impaired when compared to controls. (10) Right ventricular function has not been so well studied but is also impaired in septic shock which is not surprising since right ventricular (RV) afterload is invariably increased in septic shock since the patient is ventilated, probably has acute lung injury and will usually be on high doses of vasopressors. Right ventricular ejection fraction (RVEF) is reduced in the majority of patients but no correlation was demonstrated between the reduction in RVEF and the increase in afterload. Right

ventricular diastolic function is also impaired in septic shock (11) which probably reflects the reduced compliance due to the interstitial oedema observed at post mortem.

## **DIAGNOSIS**

### *Biomarkers*

Cardiac troponins (cTnT & cTnI) are very sensitive and specific markers of cardiac myocyte injury and are now central to the diagnosis of acute myocardial infarction. Using tissue Doppler imaging (TDI) and speckle tracking echocardiography, Landesberg et al. assessed systolic and diastolic function by global longitudinal imaging and demonstrated a correlation between LV and RV diastolic dysfunction and contemporaneous TnT levels and concluded that LV diastolic and RV systolic dysfunction seemed to explain the association between raised troponin levels and mortality in septic shock. (12)

However in an ICU setting there are many other causes of a raised troponin found in patients without a primary cardiac reason for admission and a recent study showed that 84% of patients admitted to ICU had a raised troponin level during their ICU stay. (13) Therefore although the sensitivity of troponin in patients with SC may be high, its specificity for establishing the diagnosis is poor. In a patient in whom the diagnosis of SC has been established serial troponin levels may have a role in guiding the success of therapies in limiting further myocardial damage.

Brain natriuretic peptide (BNP) is released from the ventricles in response to cardiac wall stretch and a BNP rise occurs in SC (14) but a recent study concluded that the severity of the critical illness rather than sepsis or SC specifically was the main cause of the observed BNP rise and it is therefore not useful as a predictive marker for SC. (15)

### *Echocardiography*

Conventional trans-thoracic echocardiography (TTE) has reported on volumetric measurements in septic cardiomyopathy such as LV ejection fraction and fractional shortening but these are affected by changes in LV preload and afterload and this probably explains the differing conclusions reached in earlier studies about the changes in ventricular volumes that occur in septic shock and their prognostic significance. As a result of improvements in software tech-

nology speckle tracking echocardiography (STE) has emerged as the latest method of assessing ventricular deformation in sepsis that has the advantage over conventional measurements of not being dependent on preload or afterload and over Doppler-derived indices such as the myocardial performance index (MPI) of being angle independent and much more reproducible. The portability of these more sophisticated machines also means that such studies can now be performed in the ICU at the patient's bedside. STE is based on the tracking of acoustic speckles in the myocardium and allows measurement of the change in length of myocardial segments. The main measurement calculated in STE is strain which is defined as the change in the length of the myocardial fibre at end-systole compared to its length at end-diastole. Strain can be measured in the longitudinal, radial and circumferential directions. If measurements of longitudinal strain are made in all myocardial segments, the averaged value is the global longitudinal strain (GLS) which has been validated as a highly reproducible measurement. (16) A recent study using STE in patients on the ICU with septic shock concluded that it is capable of detecting significant LV impairment which was not detectable by conventional echocardiographic techniques and also that the ventricular dysfunction is reversible in patients who survive their episode of sepsis. (17) Total isovolaemic time measures global LV electromechanical dys-synchrony & this is both common and associated with an increased mortality. Echocardiographically guided re-synchronisation therapy may significantly improve cardiac output in patients with septic shock and severe heart failure requiring high doses of vasopressors. (18) Assessment of the RV is more complex but although the tricuspid regurgitation (TR) signal is routinely interrogated to derive an estimate of pulmonary artery pressure (PAP), the duration of TR is often not considered. However TR prolongation occurs secondary to a raised PAP or a conduction defect or both and it may limit filling of both the RV and occasionally the LV and thereby limit cardiac output. If identified it allows consideration of the use of  $\beta$ -blockers or ivabradine to slow the heart although a balance has to be struck between the benefits of slowing the heart rate and the fact that stroke volume is largely fixed and cardiac output is therefore proportional to heart rate. Studies have suggested that using a short-acting  $\beta$ -blocker such as esmolol to achieve a heart rate between 80 and 95/min may be the best compromise. (19)

## PROGNOSIS

Several studies have shown that the emergence cardiovascular dysfunction in patients with septic shock increases the mortality by more than twice compared to those patients who had organ failure but without apparent cardiac involvement. (20, 21)

Early reports using conventional echocardiography suggested that increased end-diastolic volume and reduced ejection fraction was associated with an improved prognosis and could be considered as an adaptive change. However a meta-analysis of 14 studies looking at studies of ventricular volumes and dysfunction published up to 2012 has shown that survivors had lower ejection fractions and that there is no sig-

nificant differences in LVEF or RVEF or in RV dimensions between survivors and non-survivors from severe sepsis or septic shock. (22)

Brain natriuretic peptide (BNP) together with ANP, troponin and C reactive protein has been investigated in patients admitted to ICU with severe sepsis and who required mechanical ventilation and BNP was the most powerful predictor of mortality. (23)

## CONCLUSIONS

- Septic cardiomyopathy is a distinct entity characterized by impaired myocardial contractility with initially reduced preload and afterload pressures and an

impaired stroke work response to increases in the ventricular preload

- If the patient survives the episode of sepsis the myocardial changes are reversible
- Speckle tracking echocardiography is the most sensitive technique for identifying sepsis induced myocardial dysfunction
- If the diagnosis of SC is established in septic shock, the mortality is about twice that of patients without cardiac organ failure
- Further studies are required to assess alternative therapies such as heart rate control with  $\beta$ -blockers, ivabradine or biventricular pacing

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