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UNDERSTANDING THE DISEASE

Cardiac dysfunction in sepsis

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Introduction

The incidence of cardiac dysfunction in septic shock, septic cardiomyopathy, is between 40 and 60 % as diagnosed within the first 3 days [1]. Its recognition, treatment and focus for clinical research are hampered by the lack of a consensus definition. An acute or acute-on-chronic but reversible ventricular dysfunction, typically visualized at echocardiography, is generally agreed upon. The systemic nature of sepsis and the interdependence of the left (LV) and right (RV) ventricles mean that heart function is affected globally.

Septic cardiomyopathy results from the infectious process (inflammation, toxins, mitochondrial dysfunction), reduced myocardial perfusion (microthrombi, flow maldistribution) and pulmonary injury (hypoxia, hypercarbia, atelectases).

This summary highlights issues related to venous return, heart function and vascular tone. Although load-independent variables have been called for to disentangle the complexities of cardiac dysfunction in sepsis, the physiological state of ventriculo-arterial coupling challenges this approach.

Many issues are still unresolved and future research should focus on optimizing the methodology to assess septic cardiomyopathy and direct therapy (Table 1).

The treatment of septic cardiomyopathy requires cardiovascular monitoring [2], including mean arterial pressure (MAP), central venous pressure (CVP) and cardiac output (CO) ideally supported by echocardiography that provides invaluable additional information on myocardial function. The endpoint to which therapy for septic cardiomyopathy must be titrated is the resolution of shock, which may be sequentially assessed from organ function (e.g. biochemistry and SOFA score) and matching of oxygen delivery/consumption (lactate, arteriovenous O_2 and venoarterial CO_2 gradients, acid–base status) [3].

Venous return and cardiac output

Increased venous, in particular splanchnic, capacitance in sepsis leads to a reduced mean systemic filling pressure. RV dysfunction related to direct myocardial injury and/or sustained pulmonary hypertension increases CVP. Pulmonary hypertension may be induced by pulmonary vascular dysfunction [4] induced by sepsis per se or aggravated by positive pressure ventilation [5] for septic lung injury. The reduced pressure gradient for venous return results in decreased CO.

Volume expansion using crystalloids to increase venous return and hence CO remains the first-line treatment, correcting frequent absolute hypovolaemia. Its efficacy may be increased by the early administration of a vasopressor to decrease venous capacitance, treating relative hypovolaemia. Correcting hypovolaemia may unmask septic cardiomyopathy.

Beyond the stage of initial fluid loading, any further volume therapy should be guided by a corresponding increase in CO to avoid detrimental fluid overloading as the presence of vasoplegia, dysrhythmias, pulmonary hypertension, LV diastolic and RV dysfunction and ventriculo-arterial uncoupling distorts volume responsiveness.

Heart function

Depressed LV systolic function, commonly defined by reduced LV ejection fraction (LVEF), is characteristic of septic cardiomyopathy while the association between the degree of impairment and clinical outcomes is debated [6, 7]. The LVEF estimate relies on volume, and hence clearly load-dependent, changes. Ventriculoarterial coupling means that maintained LVEF is seen with persistent vasoplegia. About 20 % of septic patients demonstrate LV diastolic dysfunction [8] that may also relate to concurrent vasopressor and volume therapy. It is not always

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Table 1 Main characteristics of septic cardiomyopathy, treatment and unresolved issues

	Comment	Findings	Treatment	Unresolved issues
LV systolic dysfunction	Dependent on timing of assessment in relation to septic insult Variable association with outcomes (e.g. for LVEF) might reflect load-dependency, including ventriculoarterial coupling, or failure to consider concomitant RV dysfunction	S(c)VO_2 normal or low CO normal or low ECHO: LVEF <40–45 %, no LV enlargement, normal mitral inflow, (no increased LV filling pressure)	Dobutamine Inodilators[a]: currently being investigated VA ECMO[b]: case series reports only	When do we need to treat in the course of sepsis?
LV diastolic dysfunction	Unmasked by volume expansion and hence related to fluid management in sepsis. Can exist without concurrent systolic dysfunction	Clinical signs of congestion ECHO: *e′* (TDI) <8–10 cm/s, *E*/*e′* >12 (increase LV filling pressure in case of fluid overload)	Limit fluid administration Beta-blockers: proof of concept tested in small single-centre studies	Does it increase mortality?
RV dysfunction	Related to transpulmonary pressure gradient and pulmonary vascular resistance and hence linked to septic lung injury and mechanical ventilation	Elevated CVP Decreased CO ECHO: RV dilatation, decrease in Sm (TDI), strain/strain rate	Noradrenaline Dobutamine if concomitant LV dysfunction Inodilators/pulmonary vasodilators[a]: currently being investigated Limit airway pressure	Could its prevention improve prognosis?
Emerging echocardiographic techniques: Doppler imaging Speckle tracking echocardiography (STE); strain/strain rate	Sensitive echo modalities STE might be less operator dependent compared to TDI, but both modalities require significant expertise and are challenging during ICU conditions Still load dependent	Impaired global longitudinal strain (GLS) in systole (−ve values) and/or diastole (+ve values) LV GLS >−13 % associated with mortality, independent of LVEF changes	As per systolic and/or diastolic impairment demonstrated	What is the cut-off to start treatment? Oversensitive measurements? Agreed measurement standards lacking but are in progress

LVEF left ventricular ejection fraction, *S(c)*VO_2 mixed or central oxygen venous saturation, *CO* cardiac output, *CVP* central venous pressure, *RV* right ventricle, *LV* left ventricle, *e′* maximal velocity of the mitral annulus at the early phase of diastole, *E*/*e′* ratio of the maximal velocities during the early phase of diastole of mitral inflow and mitral annulus, *Sm* maximal velocity of the tricuspid annulus movement during systole

[a] Inodilator therapy using levosimendan has been preliminary reported to improve LV and/or RV function while adverse effects related to vasodilatation and prolonged half-time must be carefully considered

[b] Has only been reported in small series and its potential remains to be confirmed

associated with decreased LVEF and the prognostic implications of LV diastolic dysfunction are not clear [8, 9].

As mentioned, RV dysfunction is multifactorial and may be more reflective of disease severity and hence linked to clinical outcomes [10]. The presence of RV dysfunction can mask concomitant LV dysfunction.

There is increasing support for the use of speckle tracking echocardiography to investigate septic cardiomyopathy. While technically challenging in the critical care setting, this technique may allow less load-dependent assessments to be made of myocardial function.

Dobutamine remains the most commonly used inotropic agent to improve an insufficient CO following volume expansion with persisting shock, particularly when diastolic dysfunction limits the therapeutic potential of fluid resuscitation. The adverse effects of dobutamine, or other catecholaminergic stimulation, include tachycardia that in the setting of relative or absolute uncorrected hypovolaemia combined with a low afterload secondary to septic vasoplegia predisposes to left ventricular outflow obstruction. This illustrates the need for CO monitoring and/or echocardiography to guide therapy. Dobutamine has pro-inflammatory and immunodepressant effects and increases absolute mortality when used at high doses. The calcium-sensitising agent levosimendan is an inodilator with experimental studies demonstrating immunomodulatory, antiapoptotic and antioxidant properties. It might become an alternative to dobutamine given some support from a recent meta-analysis [11] and with the LeoPARDS study ongoing (ISRCTN12776039) [12].

The use of venoarterial extracorporeal membrane oxygenation (ECMO) for unresponsive cardiac dysfunction in adult septic shock, although very rare, may be considered for patients with early, severe myocardial dysfunction refractory or poorly responding to inotropic simulation.

Vascular tone and arterial pressure

An increase in cardiac afterload induced by vasopressor administration might unmask cardiac dysfunction that in the presence of a low afterload is not detectable. The hyperdynamic septic state seen in vasoplegia with a supranormal LV ejection fraction is prognostically unfavourable [13], supporting the notion that the cardiac component of septic shock could be less significant than the maldistribution of organ perfusion related to the vascular component. No evidence is available to define an optimal arterial pressure in septic shock. In the absence of pre-existing coronary disease, the cardiac dysfunction in sepsis is not simply related to coronary hypoperfusion and the diastolic pressure does not warrant any particular attention per se apart from reflecting vascular tone. Norepinephrine remains the vasopressor of choice but adding low dose vasopressin early and in less severe cases of septic shock might be considered. Tachyphylaxis to catecholamines as well as induced dysrhythmias limit the extent to which these agents can be used to elevate arterial pressure. The use of alternative vasopressors such as selepressin has attracted recent interest [14] with two clinical trials (NCT01612676, NCT01000649) to be reported. The adverse effects of individual agents may be limited by combining more than one pathway to achieve vasoconstriction.

Ventriculo-arterial coupling and heart rate

Tachycardia can exacerbate ventriculo-arterial uncoupling and hence decrease cardiovascular efficiency. Recent single-centre studies suggest that short-acting beta-blockade by esmolol in tachycardic, hyperdynamic septic patients with preserved ejection fraction might improve ventriculo-arterial coupling and stroke volume allowing for norepinephrine dosage to be reduced [15]. Whether this hypothesis is true has to be confirmed by other studies.

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