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ORIGINAL ARTICLE

Characterization of critically ill patients with septic shock and sepsis-associated cardiomyopathy using cardiovascular MRI

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Abstract

Aims Sepsis-induced cardiomyopathy is a major complication of septic shock and contributes to its high mortality. This pilot study investigated myocardial tissue differentiation in critically ill, sedated, and ventilated patients with septic shock using cardiovascular magnetic resonance (MR).

Methods and results Fifteen patients with septic shock were prospectively recruited from the intensive care unit. Individuals received a cardiac MR scan (1.5 T) within 48 h after initial catecholamine peak and a transthoracic echocardiography at 48 and 96 h after cardiac MR. Left ventricular ejection fraction was assessed using both imaging modalities. During cardiac MR imaging, balanced steady-state free precession imaging was performed for evaluation of cardiac anatomy and function in long-axis and short-axis views. Native T1 maps (modified Look–Locker inversion recovery 5 s(3 s)3 s), T2 maps, and extracellular volume maps were acquired in mid-ventricular short axis and assessed for average plane values. Patients were given 0.2 mmol/kg of gadoteridol for extracellular volume quantification and late gadolinium enhancement imaging. Critical care physicians monitored sedated and ventilated patients during the scan with continuous invasive monitoring and realized breathholds through manual ventilation breaks. Laboratory analysis included high-sensitive troponine T and N terminal pro brain natriuretic peptide levels. Twelve individuals with complete datasets were available for analysis (age 59.5 ± 16.9 years; 6 female). Nine patients had impaired systolic function with left ventricular ejection fraction (LVEF) $<$ 50% (39.8 ± 5.7%), and three individuals had preserved LVEF (66.9 ± 6.7%). Global longitudinal strain was impaired in both subgroups (LVEF impaired: 11.0 ± 1.8%; LVEF preserved: 16.0 ± 5.8%; P = 0.1). All patients with initially preserved LVEF died during hospital stay; in-hospital mortality with initially impaired LVEF was 11%. Upon echocardiographic follow-up, LVEF improved in all previously impaired patients at 48 (52.3 ± 9.0%, P = 0.06) and 96 h (54.9 ± 7.0%, P = 0.02). Patients with impaired systolic function had increased T2 times as compared with patients with preserved LVEF (60.8 ± 5.6 ms vs. 52.2 ± 2.8 ms; P = 0.02). Left ventricular GLS was decreased in all study individuals with impaired LVEF (11.0 ± 1.8%) and less impaired with preserved LVEF (16.0 ± 5.8%; P = 0.01). T1 mapping showed increased T1 times in patients with LVEF impairment as compared with patients with preserved LVEF (1093.9 ± 86.6 ms vs. 987.7 ± 69.3 ms; P = 0.03). Extracellular volume values were elevated in patients with LVEF impairment (27.9 ± 2.1%) as compared with patients with preserved LVEF (22.7 ± 1.9%; P $<$ 0.01).

Conclusions Septic cardiomyopathy with impaired LVEF reflects inflammatory cardiomyopathy. Takotsubo-like contractility patterns occur in some cases. Cardiac MR is safely feasible in critically ill, sedated, and ventilated patients using extensive monitoring and experienced staff.

Trial Registration: retrospectively registered (ISRCTN85297773)

Keywords Sepsis; Septic cardiomyopathy; Non-ischaemic cardiomyopathy; Inflammation; Septic shock; Cardiac MR; CMR

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Introduction

Sepsis is an inflammatory syndrome initiated by an inappropriate immune response to invading microorganisms, which leads to life-threatening organ dysfunction. Septic cardiomyopathy as a critical feature of sepsis-induced organ failure is associated with a significantly increased mortality rate of 50–90% compared with 20% among patients with sepsis that is not accompanied by cardiovascular impairment.[1] Although consistent diagnostic criteria are still lacking, it is known that 24–60% of patients with septic shock develop systolic heart failure with right and/or left ventricular dysfunction.[2,3]

The exact pathophysiologic mechanism of septic cardiomyopathy is yet to be fully understood; however, there is evidence of multiple molecular, metabolic, and structural changes of cardiomyocytes, which ultimately lead to transient myocardial dysfunction.[4] Animal studies showed that bacterial endotoxins might be key drivers through pathogen recognition by toll-like receptors that consecutively activate pro-inflammatory cytokine pathways. Other evidence suggests involvement of tumour necrosis factor alpha leads to interleukin release or excessive myocardial nitrogen oxide synthesis, which increase cardiac depression. Damage typically occurs via changes in endothelial permeability, leading to myocardial oedema, increased neutrophil infiltration, fibrin deposition, and even activation of the coagulation cascade.[5]

While the understanding of the molecular pathophysiology of septic cardiomyopathy is under continuous investigation, there is also need for clinical characterization of patients with septic cardiomyopathy. Understanding cardiovascular function in the setting of sepsis may be critical when it comes to treatment decisions, that is, aggressive fluid resuscitation has been an important part of sepsis therapy for decades; however, literature suggests that it may be harmful in some patients.[6]

Most clinical studies have been focused on invasive und non-invasive haemodynamic and/or functional monitoring of patients so far. Using echocardiography, it was shown that systolic cardiac dysfunction typically occurs within 48–72 h of septic shock.[2] A hallmark feature of septic cardiomyopathy is that functional abnormalities are most often reversible, with full recovery of cardiac function at 7 to 10 days after the onset of sepsis.[7,8] Temporary elevation of troponine T and brain natriuretic peptide levels are accompanying septic cardiomyopathy and reflect acute cellular and functional stress.

For further differentiation of myocardial dysfunction in patients with septic cardiomyopathy, non-invasive myocardial tissue differentiation using cardiovascular magnetic resonance (CMR) imaging can be beneficial. CMR has the unique capability not only to evaluate functional cardiac parameters but also to detect myocardial oedema, inflammation, and diffuse or focal fibrosis using T1 mapping, T2 mapping, and late gadolinium enhancement (LGE) and is increasingly established as a diagnostic tool in patients with inflammatory heart disease or secondary cardiomyopathy.[9] In suspected acute or chronic myocarditis, CMR is already considered the non-invasive diagnostic reference standard and holds prognostic value.[10,11] Furthermore, there is increasing evidence that CMR may help to diagnose and differentiate myocardial inflammation in patients with systemic inflammatory conditions such as systemic lupus erythematosus, systemic sclerosis, or sarcoidosis where cardiac involvement often occurs secondarily.[12–14] Sepsis and septic shock—as severe systemic inflammatory conditions—may also result in inflammatory myocardial changes detectable by CMR.

Given the considerable logistical and medical complexity of handling patients in septic shock, systematic CMR data in humans are, to our knowledge, limited to case reports.[15,16]

Hence, in the present pilot study, we wanted to prospectively perform myocardial tissue characterization in patients with septic shock using CMR.

Methods

Study population

A total of 15 patients were prospectively recruited on the intensive care unit (ICU) of our hospital. In order to achieve this recruitment, we screened a total of 86 patients with septic shock between April 2016 and November 2019, of which 29 patients did not qualify due to probable fatal prognosis within 48 h, 35 patients could not be recruited due to rejection of approval by their legal guardians, and 7 patients were not recruited due to absolute magnetic resonance imaging (MRI) contraindication.

Inclusion criteria were admission to the ICU due to bacterial infection with septic shock, defined as vasopressor requirement to maintain a mean arterial pressure of $\geq$65 mmHg or greater and serum lactate $>$ 2 mmol/L despite sufficient fluid resuscitation, reflecting the Third International Consensus Definitions for Sepsis and Sepic Shock. Exclusion criteria were previously known systolic heart failure with left ventricular ejection fraction (LVEF) $<$ 40%, myocardial infarction with 6 months before recruitment, acute or chronic renal failure with glomerular filtration rate $<$ 30 mL/m^2 unless patients were already on dialysis, known incompatibility for gadolinium contrast media, contraindication for MRI, and restricted therapy goals. The study was approved by the local institutional ethical review board. All enrolled individuals or their legal guardian gave written informed consent before participation.

Cardiovascular magnetic resonance protocol

The CMR scan was performed in a time window of 24–72 h after first noradrenaline peak dosage. All study participants

were examined using a 1.5 Tesla Siemens AvantoFit® scanner (Siemens Healthineers, Erlangen, Germany) with a 32-channel phased array coil. Participants received 0.2 mmol/kg of gadoteridol contrast agent (ProHance®, Bracco Diagnostics, Princeton, New Jersey) for contrast-enhanced image sequences. Left ventricular (LV) and right ventricular (RV) volumetric and functional parameters were assessed in long-axis and short-axis steady-state free precession cine sequences. Cine imaging parameters included field of view (FOV) 340 mm, voxel size 1.8 × 1.8 × 7 mm^3, 3 mm gap, echo time (TE) 1.2 ms, repetition time (TR) 33.4 ms, flip angle 74°, and bandwidth 930 Hz.

T1 mapping was performed using a modified Look–Locker inversion recovery (MOLLI) sequence in a mid-ventricular short-axis slice before and 15 min after contrast administration.[17] Sequence parameters were as follows: native T1: 5 s(3 s)3 s with FOV 360 mm, voxel size 1.6 × 1.6 × 7 mm^3, TE 1 ms, TR 339.4 ms, flip angle 35°, bandwidth 1063 Hz; post-contrast: 4 s(1 s)3 s(1 s)2 s with FOV 360 mm, voxel size 1.6 × 1.6 × 7 mm^3, TE 1 ms, TR 419.4 ms, flip angle 35°, and bandwidth 1063 Hz.

Motion-corrected T2 mapping was performed using an established T2 prepared steady-state free precession technique (three single-shot images with T2 preparation times of 0/24/55 ms and voxel size of 1.6 × 1.6 × 6.0 mm).[18]

Late gadolinium enhancement was used for focal fibrosis imaging and performed in the same slice positions as cine imaging using a gradient echo-based segmented phase-sensitive inversion recovery sequence in single-slice, single-breathhold fashion. LGE scan parameters were as follows: FOV 380 mm, voxel size 1.8 × 1.8 × 7 mm, no interslice gap, TE 1 ms, TR 700 ms, flip angle 65°, and bandwidth 1184 Hz.

Patient monitoring

At least two physicians were present during the CMR scan—one board-certified critical care medicine specialist for patient monitoring and one SCMR level III-certified cardiologist for scan surveillance. Sedated and ventilated patients were continuously monitored invasively (blood pressure) and non-invasively (pulse oximetry and heart rhythm) using MR-compatible system Expression MR400 (Philips, Amsterdam, Netherlands). Breathholds were ensured in end-inspiration using the ventilation system via manual ventilation pause. Refer to *Figure 1* for an illustrative example of the CMR setup for a sedated and ventilated individual.

Image analysis

Two experienced readers (SCMR level II and III) were blinded to clinical patient information. All image analysis was performed using cvi42® post-processing software Version 4.2 (Circle Cardiovascular Imaging Inc., Calgary, Canada). LV and RV size and function as well as LV mass were assessed in short-axis cine images, atrial volumes were assessed monoplane (right atrium) or biplane (left atrium) in long-axis cine four-chamber and two-chamber views.

Global longitudinal strain was quantified using feature tracking four-chamber-view, three-chamber-view, and two-chamber-view. Endocardial and epicardial contours were manually drawn in the end-diastolic phase, defined as the phase with the largest LV volume. Trabeculae, papillary muscles, pericardium, and epicardial fat were consequently excluded from contouring.[19]

Figure 1 Cardiovascular magnetic resonance setup for sedated and ventilated patients. (A) Positioning of MR-safe ventilators, monitoring unit, and injections pumps. (B) During the scan, an intensive care specialist monitors patient continuously in the scanner room and receives commands for end-expiratory breathhold via headphone.

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Epicardial and endocardial contours in a mid-ventricular short-axis slice were traced for T1 and T2 mapping analysis, and a 5% safety margin was applied endocardially and epicardially to minimize partial volume effects. Both T2 and T1 maps were quantified as average global values in the analysed slice according to the AHA-segment model as previously reported.[17] Visual surveys were evaluated for artefacts, and areas of LGE before quantification and segments with relevant artefacts were excluded from analysis (e.g. caused by susceptibility, unintended motion effects, or incorrect motion correction).

Relative and absolute extracellular volume (ECV) fraction was calculated by means of native and post-contrast T1 values as previously established.[17] Relative ECV was reported as percent of myocardial volume of the corresponding short-axis plane, absolute ECV in gram extrapolated towards LV mass.

Visual evaluation of LGE images was performed by two independent readers and included presence, location, and transmurality of identified lesions. Differentiation of real LGE lesions from artefacts was realized during image acquisition by verification in two perpendicular slices or altered readout direction.

Laboratory blood analysis

On the day of the CMR scan and four consecutive days after the scan, venous blood samples were obtained and immediately sent for laboratory analysis at our central laboratory. High-sensitivity cardiac troponin T (hsTnT) concentrations were measured using the Elecsys® hsTnT STAT assay (Roche Diagnostics, Mannheim, Germany). The analytical limit of detection was 5 ng/L and the 99th percentile upper reference limit was 14 ng/L.

Plasma N terminal pro brain natriuretic peptide (NT-proBNP) concentrations were measured using the Elecsys® proBNP II assay (Roche Diagnostics, Mannheim, Germany). The analytical limit of detection of NT-proBNP was 5 pg/mL.

Echocardiography

Bedside transthoracic echocardiography was performed by the same experienced cardiologist at 48 and 96 h after the CMR scan for follow-up on LVEF on a Vivid E90 system (GE Healthcare, Chicago, Illinois, USA). LVEF was assessed using biplane long-axis measurements in two-chamber and four-chamber view (modified Simpson's method).

Statistical analysis

All measured values are shown as mean ± standard deviation. We performed statistical analyses using SPSS Statistics 22.0.0 (IBM, Armonk, NY, USA). We analysed normal distribution with Kolmogorov–Smirnov test. We used the paired sample *t*-test for assessment of LVEF development. For correlation analysis, we calculated Pearson correlation coefficients. For the comparisons between subgroups (preserved vs. impaired LVEF), we used the Mann–Whitney *U*-test. A P value < 0.05 was considered to indicate a statistical significance.

Results

Patient recruitment and characteristics

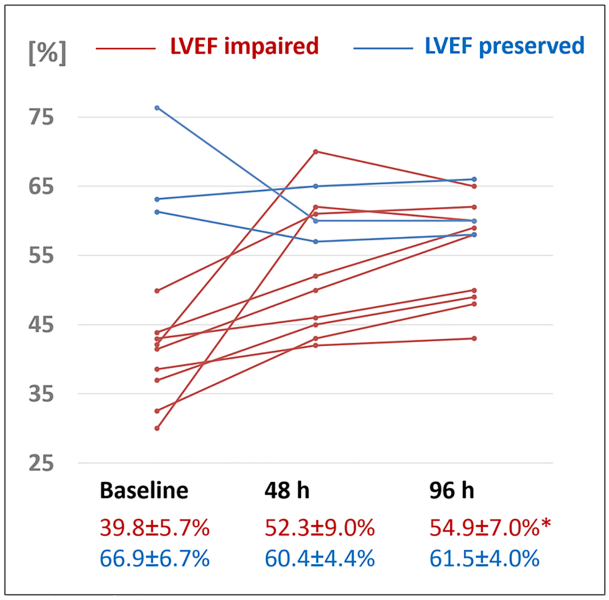
We initially recruited 15 patients. Three individuals had to be excluded due to haemodynamic instability ($n = 1$), due to excessive fluid overload with consecutive constitutional fitting issue in the scanner ($n = 1$), or due to influenza diagnosis with strict isolation requirement during the proposed scan time window ($n = 1$). Finally, we had 12 complete datasets available for analysis. Mean age of study cohort was 59.5 ± 16.9 years; six patients (50%) were female. The average Sequential Organ Failure Assessment score at admission to the ICU was 9.4 ± 2.0. In-hospital mortality was 33% and average length of stay 18.8 ± 7.9 days. All patients had an identifiable septic focus and detectable bacteria in blood cultures. Detailed characteristics of the study cohort are summarized in *Table 1*. Ten out of 12 patients (83%) were sedated,

Table 1 Patient characteristics

Age (years)	59.5 ± 16.9
Gender	6 male/6 female
Body mass index (kg/m^2)	27.5 ± 3.7
Septic focus	
Urinary tract infection	5/12 (42%)
Pneumonia	4/12 (33%)
Cholangitis	2/12 (17%)
Catheter-associated sepsis	1/12 (8%)
SOFA score at ICU admission	9.4 ± 2.0
Peak noradrenaline dose (μg/kg/min)	0.14 ± 0.05
Length of ICU stay (days)	12.3 ± 6.9
30 day mortality rate	4/12 (33%)
Blood cultures	
Escherichia coli	5/12 (42%)
Staphylococcus aureus	2/12 (17%)
Klebsiella pneumonia	1/12 (8%)
Enterococcus faecalis	1/12 (8%)
Propiobacterium acnes	1/12 (8%)
Haemophilus influenzae	1/12 (8%)
Micrococcus luteus	1/12 (8%)
Cardiovascular comorbidities	
Hypertension	4/12 (33%)
Obesity (BMI $>$ 30 kg/m^2)	3/12 (25%)
Coronary artery disease	3/12 (25%)
Type II diabetes	3/12 (25%)
Chronic heart failure	0/12 (0%)
Previous myocardial infarction	1/12 (8%)
Previous stroke	1/12 (8%)
(Ex-)Smoker	2/12 (17%)

BMI, body mass index; ICU, intensive care unit; SOFA, sequential organ failure assessment.

Figure 2 LVEF development. Data points indicate LVEF of each individual at time of cardiovascular magnetic resonance scan (baseline), at 48 and at 96 h post-cardiovascular magnetic resonance. Red data points indicate patients with LVEF impairment at baseline, and blue data points indicate patients with preserved LVEF at baseline. *$P < 0.05$ compared with baseline. LVEF, left ventricular ejection fraction.



intubated, and mechanically ventilated at the time of the CMR scan. All scans could be conducted under stable haemodynamic conditions with vasopressor support and without occurrence of any major life-threatening event. The average peak noradrenaline dosage during septic shock pre-CMR was 0.14 μg/kg/min. Dobutamine was used in one subject in addition to noradrenaline. All of the individuals received hydrocortisone and metamizole as part of the standard in-house protocol for patients with severe septic shock and ICU admission. No patient received advanced anti-inflammatory agents such as interleukin-6 antibodies or TNF-alpha antibodies. No patient was on long-term medications with immunosuppressive drugs.

Cardiovascular magnetic resonance scans could be completed within 34.0 ± 11.0 min, and there were no clinically relevant complications during scan, pre-scan preparations, or patient transport from and to the ICU.

Left ventricular and right ventricular function

At the time of the scan, nine patients (67%) had impaired systolic function with LVEF < 50% (39.8 ± 5.7%), and three individuals had preserved LVEF (66.9 ± 6.7%). All three patients with preserved LVEF died within 30 days of sepsis diagnosis, whereas 89% (8 out of 9) of individuals with impaired LVEF at CMR were successfully discharged from hospital after 24.5 ± 12.2 days.

Upon echocardiographic follow-up, LVEF improved in all previously impaired patients significantly at 48 (52.3 ± 9.0%, $P = 0.06$) and 96 h (54.9 ± 7.0%, $P = 0.02$).

Individual LVEF changes between baseline and follow-up are displayed in *Figure 2*, and detailed results of anatomical and functional parameters of all CMR studies are illustrated in *Table 2*. Notably, RVEF was also impaired in all patients with LVEF impairment (mean RVEF 38.9 ± 5.1%) while being preserved in patients whose LVEF was within normal parameters (mean RVEF 54.9 ± 2.3%).

Left ventricular GLS was decreased in all study individuals with impaired LVEF (11.0 ± 1.8%) and slightly impaired in those with normal LVEF (16.0 ± 5.8%), however, without statistically significant differences between groups ($P = 0.1$).

Contractile pattern of patients with impaired systolic function at time of CMR scan reflected global hypokinesia in seven individuals (58%) and Takotsubo-like apical hypokinesia with hyperkinetic basal segments in two individuals (17%); three patients (25%) showed normal contractility pattern. For illustrative cine imaging for each contractility category, refer to the supporting information.

Myocardial tissue differentiation

In patients with impaired systolic function, myocardial T2 times were increased at 60.8 ± 5.6 ms as compared with patients with preserved LVEF at 52.2 ± 2.8 ms ($P = 0.02$). Assessing all individuals we found a moderate negative correlation between LVEF and T2 times ($r = -0.58$; $P = 0.02$) and as well as between GLS and myocardial T2 times ($r = -0.44$; $P = 0.03$).

Native myocardial T1 mapping also revealed increased T1 times in patients with LVEF impairment (1093.9 ± 86.6 ms) as compared with patients with preserved LVEF (987.7 ± 69.3 ms) ($P = 0.03$). Correlation analysis between LVEF and native T1 times revealed a moderate to strong negative correlation with $r = -0.67$ ($P = 0.03$), while GLS and T1 times were not significantly correlated ($r = -0.31$; $P = 0.12$).

Extracellular volume analysis showed that ECV values were normal at 22.7 ± 1.9% in patients with preserved LVEF and comparatively elevated in patients with LVEF impairment at 27.9 ± 2.1% ($P < 0.01$). Refer to *Figure 3* for illustrative examples.

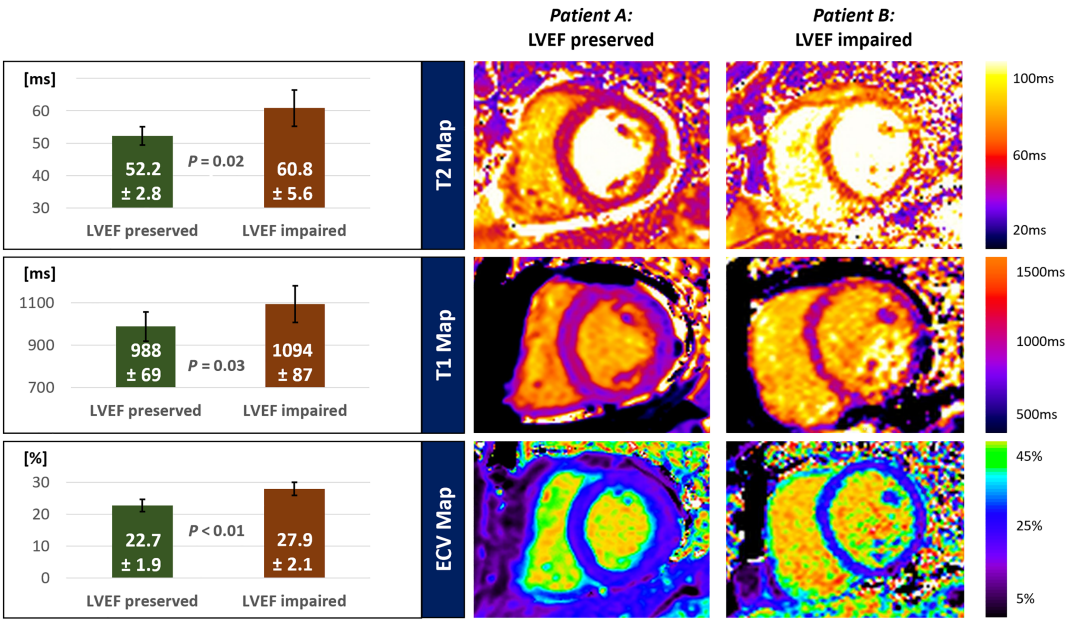
In LGE analysis, we found no signs of subepicardial enhancement in any patient. Two patients with previously known coronary artery disease had subendocardial fibrosis, but both had preserved LVEF. One patient with impaired LVEF displayed a small non-specific intramural fibrosis in the basal inferolateral myocardium.

Table 2 Cardiovascular magnetic resonance characteristics

	LVEF impaired (n = 9)	LVEF preserved (n = 3)	P value
LV end-diastolic volume (mL)	161.6 ± 40.7	142.3 ± 29.0	0.25
LV end-diastolic volume index (mL/m^2)			
LV mass (g)	121.3 ± 26.6	117.5 ± 12.6	0.42
LV mass index (g/m^2)			
LV ejection fraction (%)	39.8 ± 5.7	66.9 ± 6.7	<**0.01**
LV stroke volume (mL)	64.5 ± 19.3	94.7 ± 17.9	**0.03**
LV stroke volume index (mL/m^2)	33.7 ± 11.7	51.6 ± 7.9	**0.02**
RV end-diastolic volume (mL)	188.7 ± 47.4	146.4 ± 34.4	0.17
RV end-diastolic volume index (mL/m^2)	95.2 ± 22.4	85.1 ± 22.0	0.11
RV ejection fraction (%)	38.9 ± 5.1	54.9 ± 2.3	<**0.01**
LA volume (mL)	86.5 ± 23.5	84.6 ± 17.2	0.45
LA volume index (mL/m^2)	44.8 ± 13.8	46.1 ± 7.5	0.45
RA volume (mL)	78.2 ± 33.3	51.6 ± 11.7	0.12
RA volume index (mL/m^2)	41.2 ± 21.0	28.7 ± 7.7	0.19
LV global longitudinal strain (%)	−11.1 ± 1.77	−16.0 ± 5.8	0.10
Systolic blood pressure (mmHg)	118.1 ± 9.7	129.7 ± 25.8	0.16
Diastolic blood pressure (mmHg)	69.6 ± 9.7	69.7 ± 4.1	0.49
Heart rate (min^{-1})	77.9 ± 15.0	75.7 ± 15.5	0.42

LA, left atrial; LV, left ventricular; LVEF, left ventricular ejection fraction; RA, right atrial; RV, right ventricular.

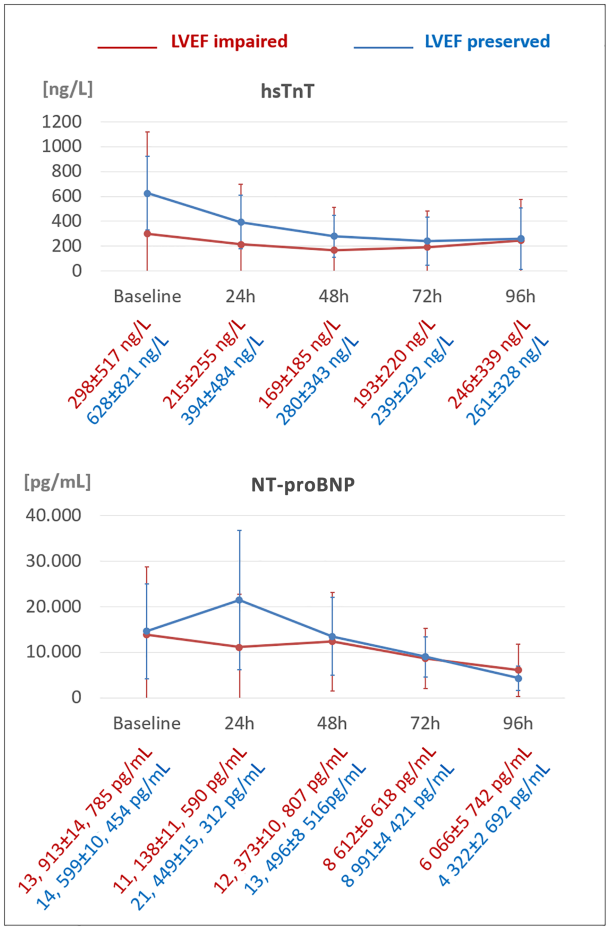
Figure 3 Tissue differentiation with T1/T2/ECV mapping. Columns represent mean T1, T2, and ECV values measured in mid-ventricular short axis for all study individuals with preserved (green) and impaired LVEF (red). *P* values indicate statistical significance. Mid-ventricular short-axis images of representative T2 maps, native T1 maps, and extracellular volume (ECV) maps of patient with and without LVEF impairment. LVEF, left ventricular ejection fraction.



Laboratory results

All patients had significantly elevated levels of hsTnT and NT-proBNP at the time of CMR scan and upon follow-up, with a wide range of individual levels. Results of hsTnT and NT-proBNP blood analysis for each timepoint are displayed in *Figure 4* and revealed no significant difference between subgroups. There was also no significant difference in peak hsTnT and NT-proBNP levels, neither between individuals with LVEF impairment and those with preserved LVEF (hsTnT: 401 ± 545 ng/L vs. 631 ± 818 ng/L; P = 0.52; NT-proBNP: 18 323 ± 15 437 pg/mL vs. 22 348 ± 14 205 pg/mL; P = 0.35) nor between individuals with and without in-hospital mortality (hsTnT: 743 ± 735 ng/L vs.

Figure 4 Blood sample analysis. Data points represent mean high-sensitivity cardiac troponin T (hsTnT) and N terminal pro brain natriuretic peptide (NT-proBNP) levels at time of cardiovascular magnetic resonance scan (baseline) and 24, 48, 72, and 96 h post-cardiovascular magnetic resonance. Red data points indicate individuals with LVEF impairment at baseline, and blue data points indicate individuals with preserved LVEF. *$P < 0.05$ compared with baseline in all subgroups. LVEF, left ventricular ejection fraction.



316 ± 541 ng/L; $P = 0.41$; NT-proBNP: 17 426 ± 14 967 pg/mL vs. 17 590 ± 14 447 pg/mL; $P = 0.88$).

Discussion

In this prospective pilot study, we evaluated myocardial tissue and function in patients with septic shock. To our knowledge, this is the first prospective assessment of patients with septic shock using CMR, most of whom were sedated, intubated, and mechanically ventilated. All scans could be completed without major complications.

We were able to detect several myocardial pathologies in our cohort. Firstly, two-thirds of patients in septic shock had LVEF and RVEF impairment at the time of CMR scan. Secondly, in these individuals with LVEF impairment during septic shock, we detected global myocardial oedema and inflammation. All patients with preserved LVEF died during their hospital stay while 89% of patients with impaired LVEF at CMR were discharged alive. Finally, hsTnT and NT-proBNP levels were elevated in all patients, irrespective of LVEF impairment.

The concept of sepsis-associated heart failure has been known for decades, but a clear definition is still lacking. In this study, we defined a temporary LVEF drop to below 50% as threshold to differentiate between groups, which is in line with previous studies and which is also used as a threshold in other non-ischaemic cardiomyopathies, that is, in anthracycline-induced cardiomyopathy.[17]

Using this threshold, we identified two-thirds of our investigated patients to have septic cardiomyopathy. Others have reported rates of 24–60%,[2] depending on definition and cohort. Cardiac MRI is considered reference standard for assessment of ventricular function and, hence, might lead to different detection rates than studies using echocardiography. Furthermore, timing of LVEF assessment is important in septic cardiomyopathy as cardiac dysfunction is known to be a dynamic and reversible process in sepsis. Previous echocardiography studies suggest that LVEF impairment typically occurs within 72 after initiation of vasopressor support, which also guided the timing in the present study.[2,20] We hypothesized that similar to other sepsis-associated organ failure (i.e. acute renal failure or acute respiratory distress syndrome), cardiac dysfunction occurs with 24 to 72 h delay to onset of septic shock. While the exact pathophysiology of septic cardiomyopathy is yet to be understood, it is known that circulatory inflammatory mediators and reactive oxygen species are acting directly on cardiomyocytes impairing calcium handling of cardiomyocytes and are leading to mitochondrial dysfunction. In addition to that, capillary leakage causes increased interstitial water content which further impairs myocardial contractility.

We detected interstitial myocardial oedema using myocardial T2 mapping and inflammation and fibrosis using native T1 mapping in most patients with septic cardiomyopathy but not in sepsis patients with preserved ejection fraction, supporting this hypothesis.

Myocardial oedema and inflammation are also detectable in acute myocarditis. Several studies on acute myocarditis report similar ranges of increased myocardial T1 and T2 times as we report here.[18,21] However, acute myocarditis with impaired systolic function often also leads to subepicardial enhancement on LGE imaging, which we have not detected in any patient of our study cohort. LGE in myocarditis is caused by irreversible necrosis of myocardial tissue, that is, due to (virus-mediated) destruction of cells and fibrotic remodelling. In contrast to that, septic cardiomyopathy is a typically

reversible phenomenon if the underlying infection can be survived, implicating that it is caused by different pathophysiologic mechanisms.[2] Francesco *et al*. published a case series on patients with septic shock and evaluation by cardiac MRI in which they found subepicardial and mid-wall LGE lesions in two out of three individuals.[22] In contrast to this study, MRI has been performed at a notably later time point (Days 28 and 49 after onset of septic shock). In our opinion, timing of the MRI is crucial in any acute-onset myocardial pathology, which is why we designed our pilot study in a way that imaging is systemically performed shortly after the haemodynamic peak of septic shock. Indeed, it is possible that also in our patient cohort, several individuals might have developed LGE lesions at a later time point. However, in analogy to viral myocarditis, LGE lesions are typically identifiable in the acute phase of the disease already, when cardiac function is mostly decreased.

Phenotypic similarities also exist between septic cardiomyopathy and Takotsubo syndrome (TTS), which is characterized by reversible cardiac dysfunction. Several pathophysiological mechanisms of TTS have been hypothesized. The description of TTS as a syndrome due to 'broken heart' suggested a critical activity of catecholamines due to acute physical or emotional stress. Increased circulating levels of these hormones, indeed, were observed by Wittstein *et al*. in a pilot study comparing patients with Takotsubo syndrome with those with acute myocardial infarction.[23] The supposed mechanisms by which catecholamine excess aggravate myocardial dysfunction, however, remain to be understood. Nevertheless, high levels of catecholamines are also present in septic shock—both host-mediated and through external therapy-related intake. Indeed, in our study, two patients showed the typical contractility pattern of TTS with apical ballooning and basal hyperkinesia. Hence, catecholamine-induced cardiac toxicity may also play a role in the pathophysiology of septic cardiomyopathy. This may even have therapeutic implications because excessive use of catecholamines in sepsis, albeit needed to a certain extent in order to maintain sufficient haemodynamics, may contribute to the development of cardiac dysfunction.

We also observed elevated ECV values in patients with septic cardiomyopathy, most likely reflecting a mixed aetiology in the acute setting: (i) due to interstitial oedema that develops due to systemic capillary leakage in sepsis and (ii) some extent of interstitial fibrosis. Some literature suggests that interstitial myocardial oedema itself can promote contractile dysfunction through misalignment of myocardial fibres, which may also explain the reversibility of LVEF impairment once the oedema is resolved.[22,24]

An interesting finding in our study cohort was that all individuals with preserved LVEF at CMR had fatal in-hospital outcomes while only one of nine individuals with initially impaired LVFE during septic shock died during their in-hospital stay. This at first counterintuitive finding maybe attributable to the small study cohort but has already been described in 1984 by Parker *et al*.[17] More recent studies have discussed, however, that septic shock patients with preserved LVEF may also be masking a decreased LV systolic function because of decreased peripheral vascular resistance leading to a hyperkinetic state of LV function. These situations were reflected in previous studies with inconsistent findings regarding the relationship between LVEF and patient prognosis.[2,3,17] In our perspective, LVEF reflects the coupling between LV contractility and LV afterload. This could lead to the phenomenon that a 'normal' LVEF may be observed in a state of severe vasoplegia (as in septic shock), despite impaired intrinsic LV contractility. Hence, LVEF analysis in septic shock is highly dependent on the state of resuscitation and on timing of the analysis. We hypothesized that the individuals with preserved LVEF and fatal outcome may have experienced a state of persistent profound vasodilatation at the time of the MRI scan, reflecting a more prolonged type of septic shock, which ultimately limited their prognosis. This hypothesis is backed by the fact that two out of three individuals had declining LVEF upon echocardiography follow-up.

If afterload impairment were the main driver of LVEF preservation in our study cohort, one might still expect to see myocardial inflammation in these individuals as their degree of septic shock may at least be as severe as in those with impaired LVEF. However, we did not see severe myocardial inflammation in patients with preserved LVEF in our study. As this is the first systematic evaluation of myocardial inflammation in septic shock using cardiac MRI, we do not have any published data to compare our results with. However, we hypothesized that this at first counterintuitive result may reflect a state of immunodeficiency in patients with prolonged septic shock, who may not be able to sustain the necessary degree of myocardial inflammation and, hence, displayed a lower degree of inflammatory parameters upon the MRI.

Blood sample analysis showed relevant troponin T and NT-proBNP levels in all study individuals irrespective of LVEF impairment. Brain natriuretic peptides are released by the atrial and ventricular myocardium in response to myocardial volume and pressure overload and ischaemic injury. Therefore, the levels of NT-proBNP are significantly elevated in heart failure and also in septic shock.[25] Furthermore, Wolff *et al*. suggested that NT-proBNP release in septic shock may only involve myocardial damage without necrosis.[26] These results are supported by our finding that no focal, previously unknown fibrosis was found on LGE imaging.

In our study, we observed significant elevations of high-sensitive troponine T as a biomarker for myocardial cell death, which is known to be elevated in patients with septic shock.[27] The absence of new focal ischaemic scars and the extent of troponin T levels in our cohort supports the established hypothesis that rather global microcirculatory myocardial ischaemia than focal coronary ischaemia plays a role in this context. Similar levels of troponin T are also reported in TTS in which absence of myocardial LGE is characteristic.

The underlying aetiology in TTS is likely related to release of catecholamines, which may contribute to troponin T release in patients with septic shock as well as described above.[28]

Limitations

There are several limitations to this study. Firstly, the study cohort was relatively small; however, the complexity of recruitment, logistics, and safety assurance of critically ill patients in septic shock is challenging. Secondly, follow-up CMR scans after full recovery from septic shock may help to differentiate between acute and chronic myocardial changes in these patients. Also, advanced invasive haemodynamic monitoring would have helped to further characterize study individuals regarding pre-load and afterload conditions. Finally, as previous LVEF data were not systematically collected for all study individuals, the acute onset of LVEF impairment in septic shock cannot be proven with full confidence. Further larger clinical studies are needed in this regard.

Conclusions

In conclusion, the present pilot study showed that (i) CMR can be performed safely also in critically ill patients with septic shock under sedation and external ventilation; (ii) myocardial oedema and inflammation, but not focal fibrosis, are hallmarks of septic cardiomyopathy with impaired LV systolic function; and (iii) the contractile phenotype is heterogeneous and may mimic TTS in some cases.

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Conflict of interest

None declared.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Supporting Information.

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