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ORIGINAL ARTICLE

Regional left ventricular systolic dysfunction associated with critical illness: incidence and effect on outcome

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Abstract

Aims Left ventricular (LV) dysfunction can be triggered by non-cardiac disease, such as sepsis, hypoxia, major haemorrhage, or severe stress (Takotsubo syndrome), but its clinical importance is not established. In this study, we evaluate the incidence and impact on mortality of LV dysfunction associated with critical illness.

Methods and results In this single-centre, observational study, consecutive patients underwent an echocardiographic examination within 24 h of intensive care unit (ICU) admission. LV systolic dysfunction was defined as an ejection fraction (EF) $<$ 50% and/or regional wall motion abnormalities (RWMA). A cardiologist assessed patients with LV dysfunction for the presence of an acute or chronic cardiac disease, and coronary angiography was performed in high-risk patients. Of the 411 patients included, 100 patients (24%) had LV dysfunction and in 52 (13%) of these patients, LV dysfunction was *not* attributed to a cardiac disease. Patients with LV dysfunction and non-cardiac disease had higher mortality risk score (Simplified Acute Physiologic Score 3 score), heart rate, noradrenaline doses, and lactate levels as well as decreased EF, stroke volume, and cardiac output compared with patients with normal LV function. Diagnoses most commonly associated with LV dysfunction and non-cardiac disease were sepsis, respiratory insufficiency, major haemorrhage, and neurological disorders. RWMA (n = 40) with or without low EF was more common than global hypokinesia (n = 12) and was reversible in the majority of cases. Twelve patients had a circumferential pattern of RWMA in concordance with Takotsubo syndrome. Crude 30 day mortality was higher in patients with LV dysfunction and non-cardiac disease compared with patients with normal LV function (33% vs. 18%, P = 0.023), but not after risk adjustment (primary outcome) {odds ratio [OR] 1.56 [confidence interval (CI) 0.75–3.39], P = 0.225}. At 90 days, crude mortality was 44% and 22% (P = 0.002), respectively, in these groups. This difference was also significant after risk adjustment [OR 2.40 (CI 1.18–4.88), P = 0.016].

Conclusions Left ventricular systolic dysfunction is commonly triggered by critical illness, is frequently seen as regional hypokinesia, and is linked to an increased risk of death. The prognostic importance of LV dysfunction in critical illness might be underestimated.

Keywords Left ventricular dysfunction; Regional wall motion abnormalities; Takotsubo syndrome; Cardiac disease; Intensive care unit; Echocardiography

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Introduction

Left ventricular (LV) dysfunction is a serious condition in the critically ill patient. This can cause low cardiac output and cardiovascular instability, leading to hypoperfusion of vital organs and contributing to multi-organ failure and death.[1–5] LV dysfunction may signify an underlying cardiac disease, such as coronary artery disease (CAD), cardiomyopathies, or myocarditis, but can be triggered by critical illness itself. It is frequently seen in sepsis and after cardiac arrest, but also in other conditions such as intracerebral catastrophes, respiratory distress, severe hypoxia, and major bleeding.[6–11] In recent years, we have learned about the Takotsubo syndrome, an acute cardiovascular syndrome associated with severe stress. LV dysfunction in critical illness is often described as regional hypokinesia that is reversible, and Takotsubo syndrome could be common in critically ill patients.[12–16]

Very few systematic studies have evaluated LV dysfunction triggered by critical illness in a general intensive care unit (ICU) population. The few studies available suggest a prevalence of LV dysfunction of 8–28% in such a population.[16–19] It is not established how this affects haemodynamics, is linked to mortality, or how this differentiates from ICU patients with a primary cardiac disease. The aim of this study was to evaluate the clinical importance of LV systolic dysfunction in critically ill patients with non-cardiac disease. We did this by estimating its frequency, pattern, and impact on haemodynamics and mortality and compared these outcomes to patients with normal LV function, as well as to patients with LV dysfunction attributed to cardiac disease.

Our hypothesis was that LV systolic dysfunction is common in critically ill patients admitted with a non-cardiac disease, is frequently seen as regional hypokinesia, and is associated with an increased risk of death.

Methods

The study protocol for this prospective single-centre observational study was approved by the Regional Ethics Committee in Gothenburg, Sweden (registration number 036-18) and registered in the international database ClinicalTrials.gov (reg no. NCT03787810).

The study was performed on 151 specific study days between 28th of May 2018 and 20th of January 2019, when resources and logistics were available. All patients admitted to the ICU on those days were included consecutively. Permission for inclusion was obtained from the patient or the patient's next of kin. Patients who agreed to participate underwent transthoracic echocardiography within 24 h of admission to the ICU. Echocardiography was performed after initial resuscitation to avoid abnormal loading condition of the LV. In those with LV dysfunction, echocardiography was repeated in 3 to 5 days, wherever feasible. If new onset LV dysfunction was found (see definition below), a cardiologist was consulted to assess whether the LV dysfunction might be attributed to acute coronary syndrome or other cardiac disease and if there was a need for further acute or sub-acute investigations, including coronary angiography. This evaluation was based on clinical presentation, electrocardiogram, pattern of hypokinesia, and levels of cardiac biomarkers. Coronary angiography was only performed when deemed clinically indicated, following an ordinary risk–benefit analysis, to avoid unnecessary potential harm.[20]

Clinical data were recorded at time of echocardiography, as described below. Time to death during the first 180 days after admission and 30 day mortality was obtained from the local ICU registry.

Definitions, recordings, and measurements

Left ventricular dysfunction was defined as having regional wall motion abnormalities (RWMA) or global hypokinesia. RWMA, in turn, was defined as having at least two hypokinetic or akinetic segments with or without an ejection fraction (EF) $<$ 50%. Global hypokinesia was defined as hypokinesia affecting all segments of the LV and an EF $<$ 50%. Patients with LV dysfunction were divided into two groups according to presumed reason for systolic dysfunction: (i) patients with *LV dysfunction and cardiac disease*, including patients with a history of CAD, heart failure, significant arrhythmias, moderate/severe valvular disease, or an acute cardiac disease upon admission; and (ii) patients with *LV dysfunction and non-cardiac disease*, including patients without a history of cardiac disease and no acute cardiac disease on admission, as assessed by a cardiologist (see above). The following parameters were recorded on admission: age, sex, medical history, reason(s) for admission according to the Simplified Acute Physiologic Score III (SAPS 3), and severity of disease measured with SAPS 3 score as well as Sequential Organ Failure Assessment score (SOFA score).[21,22] The SAPS 3 score is an ICU mortality risk score obtained on admission. It is based on medical history (e.g. chronic heart disease and malignancy), cause(s) of admission in each organ system (e.g. cardiac arrest, respiratory failure, and neurological disorders), and physiologic and laboratory variables (e.g. blood pressure, heart rate, leucocyte count, and serum creatinine levels). The SOFA score is registered daily and measures the severity of multi-organ failure in ICU patients based on clinical and laboratory data in six organ systems (respiration, circulation, coagulation, liver, renal, and neurological status). Furthermore, suspected or verified sepsis, septic shock, and cardiac arrest or acute myocardial infarction were registered separately, as these diagnoses were considered important and could appear concomitant with other reasons for admission.[23] At the time of

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echocardiography, blood pressure, heart rate, dose of vasopressor, dose of inotropic support, lactate levels, serum creatinine levels, ventilator settings, and PaO_2/FiO_2 ratio were recorded.

Echocardiography was performed according to current recommendations.[24] Examinations were primarily performed with a Vivid S70 ultrasound system with a M5Sc-D matrix array transducer and to a lesser extent with a Logiq E9 system (GE Healthcare, Milwaukee, Wisconsin). Examinations were assessed offline with the EchoPac software (GE Healthcare, Milwaukee, Wisconsin). The first author (O. C.) performed the vast majority of examinations. All examinations with LV pathology, as judged by the primary examiner (O. C.) and a blinded number of normal examinations (n = 46), were reviewed by a second expert in echocardiography (O. B.-H.). Inter-agreement between the reviewers was 93% (kappa value 0.84). Any discrepancies were resolved by discussion and consensus. No examination judged as normal by the primary examiner was cited as having pathology by the second review. The echocardiographic measurements used in the study were LV EF, presence and location of RWMA, velocity time integral (VTI) in the LV outflow tract, stroke volume, and cardiac output. EF was measured by Simpson Biplane and, if not feasible, by eyeballing. RWMA was assessed using the standard 17-segment model.[25]

Intensive care unit setting(s)

The study was performed at the general and neuro ICU of a tertiary university hospital. The hospital is a tertiary centre for major trauma, major vascular and upper abdominal surgery, spinal surgery, radiological interventions, and hepatic failure, including liver transplantation. It is also a centre for coronary revascularization, embolectomy for acute stroke, and haematological stem cell transplantation. The neuro ICU treats patients with acute neurosurgical and neurological disorders such as status epilepticus, cerebral haemorrhage, and traumatic brain injury. Patients from the local area with unselected acute admissions are treated along with the tertiary care patient population in the general ICU. Acute cardiac conditions are mainly treated in the cardiac care unit but are admitted to the general ICU if at risk of, or in need of, mechanical ventilation. Patients in need of cardiothoracic surgery are admitted to the cardiothoracic ICU and were not included in the study.

Power analysis, outcomes, and statistics

A power analysis that was based on a retrospective study revealed that 400 subjects would be necessary to detect a difference in mortality between patients with LV dysfunction and non-cardiac disease compared with patients with normal LV function.[14] Details of this power analysis are presented in Supporting Information, *Data S1*.

The pre-defined primary outcome was 30 day mortality in patients with LV dysfunction and cardiac disease vs. patients with normal LV function. The risk of death was increased up to 90 days after admission, and secondary mortality analyses were performed at this time. Secondary outcomes were the frequency of cardiac disease and non-cardiac disease among patients with LV dysfunction, the frequency of patients with regional hypokinesia, or global LV dysfunction among patients with LV dysfunction. Finally, haemodynamic data in patients with vs. without LV dysfunction and its impact on mortality were evaluated.

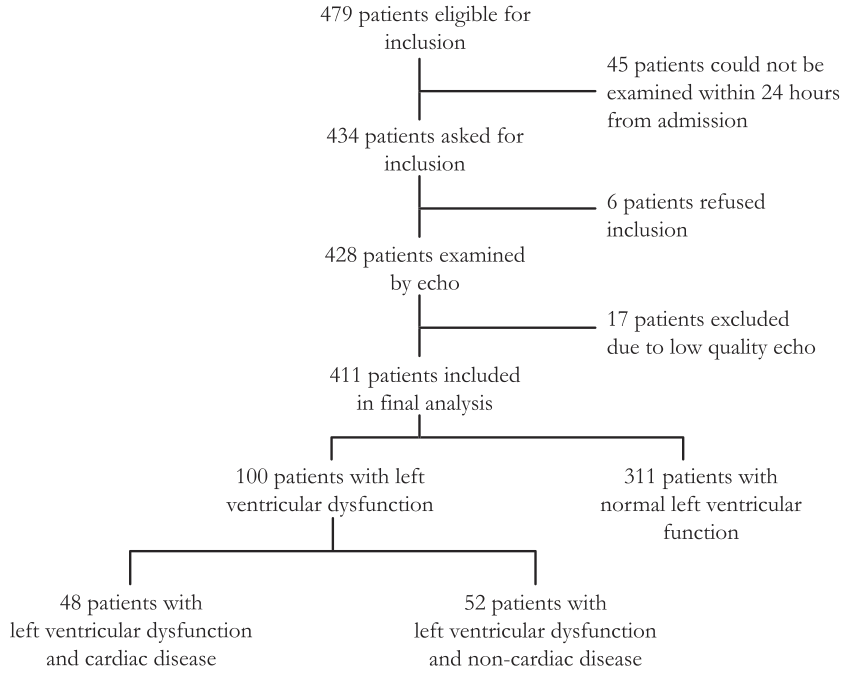
A statistical analysis plan was written before analyses were performed. Normally distributed variables are presented as the mean ± standard deviation, and non-normally distributed variables are presented as the median [interquartile range (IQR)]. The ANOVA or t-test was used for comparison of means on normally distributed variables, and the Kruskal–Wallis or Mann–Whitney U test was used for comparison of distributions of non-normally distributed variables. The χ^2 test was used for comparison of nominal outcomes between groups. Logistic regression was used for calculation of the risk of death at 30 and 90 days between patients with and without LV dysfunction in a crude and risk-adjusted analysis. Risk adjustments were performed with SAPS 3 score and age by including these variables in the logistic regression model with the exposure variable to be tested. Kaplan–Meier methodology with the log rank test was used to compare incidences during 90 days from admission. A P-value < 0.05 was considered significant. IBM SPSS Version 24.0 (IBM, Armonk, New York) was used for the statistical analyses.

Results

A total of 479 patients were eligible for inclusion in the study. In total, 68 patients were excluded: 45 were not examined by echocardiography within 24 h of admission, 6 patients declined inclusion, and for 17, echocardiography was not technically feasible, or the quality of the examinations was inadequate for analysis. Thus, 411 patients were included in the final analysis (*Figure 1*). In a sensitivity analysis, there were no differences in SAPS score, age, and 30 day mortality in the study population compared with the entire ICU population during the study period. Median time from admission to echocardiography was 11.5 h (IQR 4–17).

Of the 411 included patients, 100 had LV dysfunction (24%). Among those, 28 (7%) had a history of cardiac disease and 20 (5%) were admitted with acute cardiac disease. These 48 patients were classified as LV dysfunction and cardiac disease. In total, 52 patients (13%) were admitted with

Figure 1 Study flow chart.



non-cardiac illness and were classified as LV dysfunction and non-cardiac disease (*Figure 1*).

Patients with LV dysfunction had higher SAPS 3 and SOFA scores and were more often admitted for cardiovascular conditions, compared with patients with normal LV function. Moreover, patients with LV dysfunction and cardiac disease were older, had a higher prevalence of cardiac or peripheral artery disease, and had more frequently been admitted for respiratory issues. Patients with LV dysfunction and non-cardiac disease were more often admitted for gastroenterological conditions (*Table 1*).

Patients with LV dysfunction had lower systolic blood pressure, higher lactate levels, and higher noradrenaline doses vs. patients with normal LV function. Furthermore, patients with LV dysfunction and non-cardiac disease had a lower mean arterial blood pressure and a higher heart rate, as well as elevated central venous pressure (CVP), compared with patients with normal LV function (*Table 2*).

Mean EF was 61 ± 6% in patients with normal LV function. Patients with LV dysfunction and non-cardiac disease had a lower EF (46 ± 10%, $P < 0.001$), and the lowest EF was seen in patients with LV dysfunction and cardiac disease (39 ± 12%, $P < 0.001$). Measurement of stroke volumes and cardiac index were possible in 366 patients. Patients with LV dysfunction, regardless of being in the cardiac or non-cardiac disease group, had lower VTI, indexed stroke volumes, and cardiac index than patients with normal LV function (*Table 2*). Regional hypokinesia, with or without low EF, was more common than global hypokinesia and was seen in 82 patients (20%) of the total population and in 40 (77%) of the patients with LV dysfunction and non-cardiac disease (*Table 2*). In the patients with LV dysfunction and non-cardiac disease, apical and septal segments were most frequently affected (Supporting Information, *Data S1*). Of those patients, 12 had the typical circumferential patterns of hypokinesia seen with Takotsubo syndrome, while the other 30 patients had different patterns of RWMA. Details of pattern of RWMA are presented in Supporting Information, *Data S1*.

Of the 52 patients in our study with LV dysfunction and non-cardiac disease, 11 high-risk patients underwent coronary angiography that showed normal coronary arteries. Another two patients that initially were included in this group had coronary angiogram performed showing CAD and were thereafter classified in the cardiac disease group. In the remaining 41 patients, coronary angiography was considered not indicated due to low likelihood of CAD based on risk factors, clinical presentation, electrocardiogram, cardiac biomarkers, normalization of cardiac dysfunction, or poor prognosis. A total of 38 patients with LV dysfunction and non-cardiac disease had a follow-up echocardiogram. Eight patients were lost to follow-up because of early discharge, and six patients died shortly after admission. In the 38 patients who had a follow-up echocardiogram, complete or near complete recovery of LV function was seen in 36 of them. Median time to verified normalization was 11 [IQR 3–104] days. In the two patients without normalization, one died after 6 days without improvement, and the other patient did not normalize cardiac function within 10 days and

Table 1 Baseline characteristics of the study population

Category	Variable	Normal left ventricular function (n = 311)	Left ventricular dysfunction		P-value
			Cardiac disease (n = 48)	Non-cardiac disease (n = 52)	
Demographics	Age, years	64 (51–73)[b]	72 (58–78)[a,c]	64 (53–74)[b]	0.006
	Women, n (%)	132 (42)	17 (35)	16 (31)	0.219
Medical history	Any cardiac disease, n (%)	30 (10)[b]	28 (58)[a,c]	0 (0)[d]	<0.001
	Heart failure, n (%)	8 (3)[b]	11 (23)[a,d]	0 (0)[d]	<0.001
	Coronary artery disease, n (%)	24 (8)[b]	18 (38)[a,d]	0 (0)[d]	<0.001
	Arrhythmia, n (%)	29 (9)[b]	9 (19)[a,c]	0 (0)[d]	0.038
	Valvular disease, n (%)	4 (1)	3 (6)	0 (0)	0.060
	Hypertension, n (%)	99 (32)[b]	22 (47)[a,c]	11 (21)[b]	0.030
	Diabetes, n (%)	57 (18)	9 (19)	3 (6)	0.075
	Hyperlipidaemia, n (%)	29 (9)	6 (13)	1 (2)	0.135
	Peripheral artery disease, n (%)	12 (4)[b]	7 (15)[a]	5 (10)	0.006
	Pulmonary disease, n (%)	30 (10)	7 (15)	7 (13)	0.435
	Renal disease, n (%)	18 (6)	5 (11)	1 (2)	0.194
	Liver disease, n (%)	36 (12)	1 (2)	2 (4)	0.370
	Malignancy, n (%)	36 (12)	3 (6)	6 (11)	0.800
	Other, n (%)	155 (37)	14 (29)	19 (37)	0.401
Risk score	SAPS 3 score	57 ± 16[b,c]	64 ± 14[a]	63 ± 17[a]	0.002
	SOFA at Day 1	7 (4–9)[c]	8 (4–11)	8 (6–10)[a]	0.031
Reason(s) for admission according to SAPS 3	Cardiovascular, n (%)	115 (37)[b,c]	37 (77)[a]	34 (64)[a]	<0.001
	Cardiac arrest, n (%)	21 (7)[b]	16 (34)[a,c]	7 (13)[b]	<0.001
	Circulatory shock, n (%)	47 (15)[c]	8 (17)[c]	23 (42)[a,b]	<0.001
	Cardiac reason, n (%)	14 (4)[b]	6 (13)[a,c]	1 (2)[b]	0.035
	Other, n (%)	33 (11)	6 (13)	3 (6)	0.485
	Hepatic, n (%)	37 (12)	1 (2)	5 (10)	0.133
	Gastrointestinal, n (%)	28 (9)[c]	1 (2)[c]	13 (25)[a,b]	<0.001
	Neurological, n (%)	103 (33)	15 (32)	11 (21)	0.258
	Renal, n (%)	41 (13)	7 (15)	8 (15)	0.862
	Respiratory, n (%)	102 (33)[b]	25 (51)[a]	21 (40)	0.018
	Haematological, n (%)	12 (4)	0 (0)	4 (8)	0.134
	Metabolic, n (%)	49 (16)	12 (26)	14 (27)	0.054
	Trauma, n (%)	37 (12)	3 (6)	3 (6)	0.266
	Other, n (%)	27 (9)	3 (6)	1 (2)	0.231
Surgical status	Acute surgery, n (%)	100 (32)	16 (33)	19 (36)	0.920
	Elective surgery, n (%)	34 (11)	2 (4)	4 (8)	0.192
Other factors	Suspected or verified sepsis, n (%)	95 (30)	11 (21)	20 (38)	0.333
	Septic shock, n (%)	32 (10)	5 (9)	11 (21)	0.144
	Cardiac arrest, n (%)	23 (7)[b]	16 (34)[a,c]	7 (13)[b]	<0.001
	Acute myocardial infarction, n (%)	9 (3)	19 (40)[a,c]	0 (0)	<0.001

SAPS, Simplified Acute Physiologic Score; SOFA, Sequential Organ Failure Assessment.
P-value was calculated for detection of significance between the three groups with χ^2 test, ANOVA, or Kruskal–Wallis test, as appropriate.
[a]$P < 0.05$ vs. group normal.
[b]$P < 0.05$ vs. group cardiac disease.
[c]$P < 0.05$ vs. group non-cardiac disease.
[d]Statistics not possible to calculate due to zero observations.

was later lost to follow-up. Main reasons for admission are presented in *Table 3*. Patients with LV dysfunction and non-cardiac disease were most commonly admitted due to sepsis, respiratory failure, or major haemorrhage.

Thirty-day mortality (primary outcome) was higher in patients with LV dysfunction and non-cardiac disease (n = 17, 33%) vs. patients with normal LV function (n = 56, 18%, P = 0.023). However, this was not significant when adjusting for SAPS 3 score and age {odds ratio [OR] 1.56 [confidence interval (CI) 0.75–3.39], P = 0.225}. The secondary mortality analyses were performed at 90 days from admission. At this time, mortality was 44% (n = 23) in patients with LV dysfunction and non-cardiac disease and 22% (n = 68) in patients with normal LV function (P = 0.002). Risk-adjusted mortality at 90 days was higher in patients with LV dysfunction and non-cardiac disease compared with patients with normal LV function [OR 2.40 (CI 1.18–4.88), P = 0.016]. No differences appeared in 90 day mortality in patients with LV dysfunction and cardiac vs. non-cardiac disease (P = 0.606). Patients with RWMA [OR 2.55 (CI 1.43–4.56), P = 0.002], but not patients with global hypokinesia (P = 0.302), had an increased risk of death compared with patients with normal LV function. Of the cardiac function variables, a low stroke volume, VTI, and cardiac index were, in contrast to a low LV EF, associated with an increased risk of 90 day death in crude and risk-adjusted analyses. Mortality was highest for patients with both LV dysfunction and a low cardiac index (*Table 4*, *Figure 2*).

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Table 2 Echocardiographic, haemodynamic, and respiratory data at time of echocardiography

Category	Variable	Normal left ventricular function (n = 312)	Left ventricular dysfunction		P-value
			Cardiac disease (n = 48)	Non-cardiac disease (n = 52)	
Echocardiographic data	LV end-diastolic diameter, cm	4.8 ± 0.5[b]	5.5 ± 1.0[a,c]	4.9 ± 0.7[b]	<0.001
	LV ejection fraction, %	60 ± 6[b,c]	39 ± 12[a,c]	46 ± 10[a,b]	<0.001
	Velocity time integral, cm^2	19 ± 9[b,c]	14 ± 7[a]	14 ± 6[a]	<0.001
	Stroke volume index, mL/m^2	44 ± 12[b,c]	31 ± 12[a]	32 ± 10[a]	<0.001
	Cardiac index, $L/min/m^2$	3.5 ± 1.2[b,c]	2.6 ± 1.0[a]	2.8 ± 0.8[a]	<0.001
	Patients with RWMA, n (%)	0 (0)[b,c]	40 (85)[a]	42 (81)[a]	<0.001
	Segments with hypokinesia, n	0 (0–0)[b,c]	6 (3–12)[a,c]	5 (2–7)[a,b]	<0.001
	Wall motion score index	1 (1–1)[b,c]	1.35 (1.18–1.94)[a,c]	1.29 (1.18–1.59)[a,b]	<0.001
Haemodynamic data	Mean arterial pressure, mmHg	79 ± 14[c]	77 ± 17	74 ± 12[a]	0.037
	Systolic blood pressure, mmHg	123 ± 24[b,c]	112 ± 28[a]	109 ± 20[a]	<0.001
	Diastolic blood pressure, mmHg	59 ± 12	61 ± 19	56 ± 10	0.243
	Heart rate, b.p.m.	83 ± 21[c]	88 ± 23	91 ± 22[a]	0.038
	Noradrenaline, μg/kg/min	0 (0–0.13)[b,c]	0.10 (0–0.24)[a]	0.15 (0.06–0.3)[a]	<0.001
	CVP, mmHg	7 (4–11)[c]	10 (9–15)	12 (9–16)[a]	<0.001
	S-Lactate, mmol/L	1.3 (1.0–1.9)[b,c]	1.9 (1.2–2.5)[a]	1.5 (1.2–2.9)[a]	0.001
Respiratory data	PaO_2/FiO_2 ratio	39 (29–51)	32 (26–46)	38 (23–48)	0.209
	Mechanical ventilation, n (%)	128 (59)	23 (51)	21 (60)	0.567

CVP, central venous pressure; LV, left ventricular; RWMA, regional wall motion abnormalities.
Segments of hypokinesia and wall motion score index (WMSI) were calculated for the patients with regional hypokinesia.
P-value was calculated for detection of significance between three groups with χ^2 test, ANOVA, or Kruskal–Wallis test, as appropriate.
[a]$P < 0.05$ vs. group 'normal'.
[b]$P < 0.05$ vs. group 'cardiac disease'.
[c]$P < 0.05$ vs. group 'non-cardiac disease'.

Discussion

The main findings of this study were as follows: (i) LV systolic dysfunction is common in the critically ill patients without a primary cardiac disease; (ii) regional hypokinesia is more common than global hypokinesia in this group and is frequently reversible; and (iii) LV systolic dysfunction in the critically ill is associated with an increased risk of death that may be partly mediated by a reduced cardiac output.

To our knowledge, there is only one study that has assessed the prevalence of LV dysfunction in ICU patients with non-cardiac disease, reporting an RWMA incidence of 12% and a global LV dysfunction of 8% in patients in a medical ICU.[18] Other studies, focusing on finding specific types of LV dysfunction, or not reporting its potential cause, have found a prevalence of LV dysfunction of 8–28%.[15–17,19] In our study, we found that nearly one in four patients, in a general ICU population, had LV dysfunction. More than half of those patients were admitted with non-cardiac illness. Thus, the incidence of LV dysfunction in patients with non-cardiac disease was almost 15%. Although the subject is not widely studied, we find it likely that LV dysfunction attributed to critical illness is relatively common with a prevalence of 10–20%.

Notably, regional hypokinesia was the most common type of LV dysfunction in patients with non-cardiac disease that is seen in over 80% of the cases. Several studies have earlier reported on the presence RWMA in ICU patients with non-cardiac disease.[12–17,26] We find it less likely that this was caused by CAD because all patients with LV dysfunction were assessed by a cardiologist for the diagnosis of acute coronary syndrome. Moreover, most patients who did undergo coronary angiography had normal coronary arteries, and patients with follow-up echocardiogram had a rapid recovery of cardiac function, usually within days, which is not seen in myocardial infarction without coronary intervention.[27] In our study, we identified 12 patients (3%) with apical or midventricular hypokinesia, in concordance with typical Takotsubo, which is an incidence in agreement with other ICU-oriented studies focusing on this subject,[14,15,28] although some studies have reported higher numbers.[17]

However, most patients with RWMA and non-cardiac disease in our study did not present with such a typical pattern; rather, focal or segmental RWMAs were most common. It is plausible that this represents a stress-induced cardiomyopathy or an atypical focal phenotype of Takotsubo syndrome. Critically ill patients are subject to severe stress, and all patients in the present study had accepted physical triggers of Takotsubo syndrome. Furthermore, they fulfil the criteria for Takotsubo as having transient RWMA. Typical characteristics (e.g. female overrepresentation) was missing in the population, but Takotsubo triggered by other disease have a different clinical presentation.[11,29–31] However, the nature of transient RWMA in critical illness needs to be further explored, to verify this hypothesis.

Irrespective of the pathogenesis behind LV dysfunction in our study population, these patients had a near two-fold increased mortality. The reasons behind this increased mortality cannot be casually explained with the current study

Table 3 Main diagnoses of intensive care unit admission in patients with left ventricular dysfunction

Cardiac disease status	Diagnosis	*N*
Non-cardiac disease (n = 52)	Sepsis	10
	Respiratory insufficiency	9
	Gastrointestinal bleeding	7
	Hypoxic cardiac arrest	5
	Post-operative, major bleeding	3
	Status epilepticus	3
	Acute abdomen	3
	Aortic rupture	3
	Major trauma	2
	TBI without other injuries	2
	Subarachnoid haemorrhage	1
	Aortic occlusion	1
	Pancreatitis	1
	Liver failure	1
	Hyponatraemia	1
New onset of cardiac disease (n = 20)	AMI + cardiac arrest	8
	AMI + cardiogenic shock	4
	Cardiac arrest + new onset DCM	4
	AMI + acute abdomen	1
	Hypertensive crisis	1
	Dermatomyositis	1
	Cardiac arrest with primary arrhythmia	1
History of cardiac disease (n = 28)	Respiratory insufficiency	8
	Cardiac arrest	4
	Post-operative	4
	Aortic rupture	2
	Cerebrovascular event	3
	Sepsis	3
	Acute abdomen	1
	AMI	1
	AV-block III	1
	Hyponatraemia	1

AMI, acute myocardial infarction; AV, atrioventricular; DCM, dilated cardiomyopathy; TBI, traumatic brain injury.

design. We can, nonetheless, show that patients with LV dysfunction had a more severe disease, higher SAPS 3 and SOFA score, as well as a greater degree of haemodynamic instability with increased doses of noradrenaline, lower stroke volumes and cardiac index, as well as higher lactate levels as an indirect sign of hypoperfusion. Low cardiac output and organ hypoperfusion might lead to multi-organ failure and death. However, mortality was also increased in patients with LV dysfunction and preserved cardiac output. LV dysfunction could be a part of multi-organ failure and, thus, a marker for a more severe disease. A cardiac event triggered by critical illness could potentially increase the risk of short-term cardiovascular deaths; this would be in line with the finding that there were no differences in mortality between patients with LV dysfunction attributed to a cardiac or non-cardiac disease. Patients with a combination of LV dysfunction and low cardiac index had the highest mortality indicating that cardiogenic shock, concomitant to other disorders, is still a very serious condition in critically ill patients.

The main limitation of our study was the lack of invasive diagnostics for CAD in the majority of the patients with regional hypokinesia. Another limitation may be the assessment of LV performance with EF and RWMA, whereas other results could potentially have been found if dysfunction had been sought with, for example, speckle tracking and measurement of ventricular strain. However, estimation of LV systolic function by EF is still the recommended practice, and the possible benefits of other methods in an intensive care setting are not yet defined.[32,33] The main strengths of the study were the large sample size and the fact that the patient cohort represented a mixed ICU population. In addition, echoes were assessed by a second blinded reviewer, thus presumably rendering high validity.

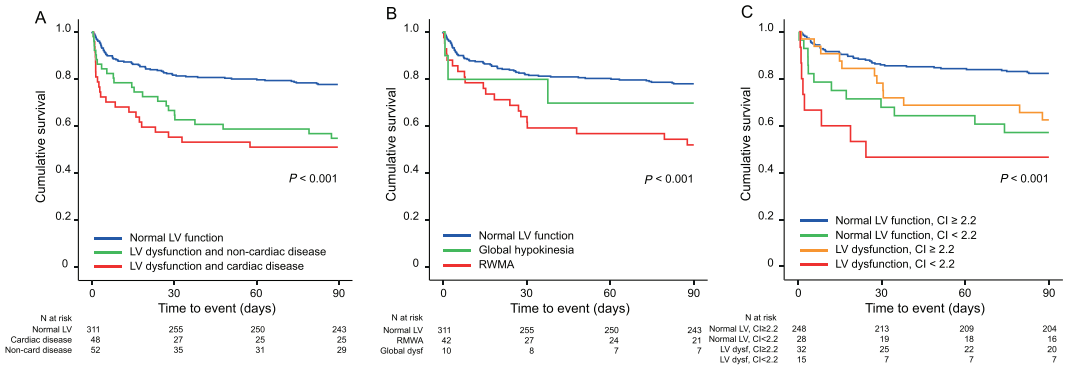
In conclusion, LV dysfunction is common in critically ill patients admitted with non-cardiac disease and is linked to an increased mortality. Although the pathogenesis is not clear, it is a risk marker that needs to be recognized. While haemodynamic assessment is clinical routine in critically ill patients, the importance of LV dysfunction might be underestimated. Further research is needed to evaluate the nature of regional hypokinesia in patients with non-cardiac illness, as well as to clarify how to optimize treatment for these patients.

Table 4 Impact of left ventricular dysfunction and haemodynamic variables on death at 90 days from admission

	Crude analysis			Risk-adjusted analysis[a]		
	OR	95% CI for OR	*P*-value	OR	95% CI for OR	*P*-value
LV dysfunction and						
Cardiac disease[b]	3.29	1.76–6.15	<0.001	2.49	1.22–5.06	0.012
Non-cardiac disease[b]	2.83	1.54–5.22	0.001	2.42	1.17–4.97	0.016
Pattern of LV dysfunction in patients with non-cardiac disease						
RWMA[b]	3.49	2.10–5.79	<0.001	2.55	1.43–4.56	0.002
Global dysfunction[b]	1.49	0.51–4.37	0.469	1.95	0.55–6.93	0.302
Cardiac function variables						
LV EF, per 10%	0.66	0.55–0.81	<0.001	0.79	0.58–1.08	0.135
Velocity time integral, per cm^2	0.94	0.92–0.97	<0.001	0.91	0.86–0.96	<0.001
Indexed stroke volumes, per mL/m^2	0.95	0.93–0.97	<0.001	0.95	0.93–0.98	<0.001
Cardiac index, per $L/min/m^2$	0.68	0.54–0.86	0.001	0.73	0.56–0.95	0.020

CI, confidence interval; EF, ejection fraction; LV, left ventricular; OR, odds ratio; RWMA, regional wall motion abnormalities.
[a]Adjusted for Simplified Acute Physiologic Score 3 score and age.
[b]Normal LV function is the reference group.

Figure 2 Mortality over time in patients with normal LV function vs. patients with LV dysfunction and cardiac or non-cardiac disease (A). Mortality over time in patients with normal LV function, global hypokinesia, and regional hypokinesia in patients with non-cardiac disease (B). Mortality over time in patients with normal LV function, LV dysfunction, and normal or low cardiac index (C). No cases were censored during the study period. CI, cardiac index; LV, left ventricular; RWMA, regional wall motion abnormalities.



Conflict of interest

J.O. received funding from the Swedish Heart-Lung Foundation, the Swedish government and county councils (the ALF agreement), the Foundation of Ollie and Elof Ericsson, and the Emelle Foundation for the conduct of this study. None of the other authors have any conflicts of interest to declare.

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Supporting information

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

Data S1. Supporting Information.

References

1. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, Gonzalez-Juanatey JR, Harjola V-P, Jankowska EA. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2016; **37**: 2129–2200.
2. Harjola VP, Lassus J, Sionis A, Køber L, Tarvasmäki T, Spinar J, Parissis J, Banaszewski M, Silva-Cardoso J, Carubelli V, Di Somma S, Tolppanen H, Zeymer U, Thiele H, Nieminen MS, Mebazaa A. Clinical picture and risk prediction of short-term mortality in cardiogenic shock. *Eur J Heart Fail* 2015; **17**: 501–509.
3. Puymirat E, Fagon JY, Aegerter P, Diehl JL, Monnier A, Hauw-Berlemont C, Boissier F, Chatellier G, Guidet B, Danchin N, Aissaoui N. Cardiogenic shock in intensive care units: evolution of prevalence, patient profile, management and outcomes, 1997–2012. *Eur J Heart Fail.* 2017; **19**: 192–200.
4. Duchnowski P, Hryniewiecki T, Koźma M, Mariusz K, Piotr S. High-sensitivity troponin T is a prognostic marker of hemodynamic instability in patients undergoing valve surgery. *Biomarkers Med.* 2018; **12**: 1303–1309.
5. Duchnowski P, Hryniewiecki T, Kuśmierczyk M, Szymanski P. Red cell distribution width as a predictor of multiple organ dysfunction syndrome in patients undergoing heart valve surgery. *Biol Open.* 2018; **7**: bio036251.
6. Ehrman RR, Sullivan AN, Favot MJ, Sherwin RL, Reynolds CA, Abidov A, Levy PD. Pathophysiology, echocardiographic evaluation, biomarker findings, and prognostic implications of septic cardiomyopathy: a review of the literature. *Crit Care.* 2018; **22**: 112.
7. Cha KC, Kim HI, Kim OH, Cha YS, Kim H, Lee KH, Hwang SO. Echocardiographic patterns of postresuscitation myocardial dysfunction. *Resuscitation.* 2018; **124**: 90–95.
8. Oras J, Grivans C, Dalla K, Omerovic E, Rydenhag B, Ricksten SE, Seeman-Lodding H. High-sensitive troponin T and N-Terminal pro B-type natriuretic peptide for early detection of stress-induced cardiomyopathy in patients with subarachnoid hemorrhage. *Neurocritical care.* 2015; **23**: 233–242.
9. Tinè M, Bazzan E, Semenzato U, Biondini D, Cocconcelli E, Balestro E, Casara A, Baraldo S, Turato G, Cosio MG, Saetta M. Heart failure is highly

prevalent and difficult to diagnose in severe exacerbations of COPD presenting to the emergency department. *J Clin Med*. 2020; **9**: 2644.
10. Bashir R, Padder FA, Khan FA. Myocardial stunning following respiratory arrest. *Chest* 1995; **108**: 1459–1460.
11. Templin C, Ghadri JR, Diekmann J, Napp LC, Bataiosu DR, Jaguszewski M, Cammann VL, Sarcon A, Geyer V, Neumann CA, Seifert B, Hellermann J, Schwyzer M, Eisenhardt K, Jenewein J, Franke J, Katus HA, Burgdorf C, Schunkert H, Moeller C, Thiele H, Bauersachs J, Tschope C, Schultheiss HP, Laney CA, Rajan L, Michels G, Pfister R, Ukena C, Bohm M, Erbel R, Cuneo A, Kuck KH, Jacobshagen C, Hasenfuss G, Karakas M, Koenig W, Rottbauer W, Said SM, Braun-Dullaeus RC, Cuculi F, Banning A, Fischer TA, Vasankari T, Airaksinen KE, Fijalkowski M, Rynkiewicz A, Pawlak M, Opolski G, Dworakowski R, MacCarthy P, Kaiser C, Osswald S, Galiuto L, Crea F, Dichtl W, Franz WM, Empen K, Felix SB, Delmas C, Lairez O, Erne P, Bax JJ, Ford I, Ruschitzka F, Prasad A, Luscher TF. Clinical features and outcomes of Takotsubo (Stress) cardiomyopathy. *New Engl J Med*. 2015; **373**: 929–938.
12. Sharkey SW, Shear W, Hodges M, Herzog CA. Reversible myocardial contraction abnormalities in patients with an acute noncardiac illness. *Chest* 1998; **114**: 98–105.
13. Oras J, Doueh R, Norberg E, Redfors B, Omerovic E, Dellgren G. Left ventricular dysfunction in potential heart donors and its influence on recipient outcomes. *J Thoracic Cardiovasc Surgery*. 2020; **159**: 1333–1341.e1336.
14. Oras J, Lundgren J, Redfors B, Brandin D, Omerovic E, Seeman-Lodding H, Ricksten SE. Takotsubo syndrome in hemodynamically unstable patients admitted to the intensive care unit - a retrospective study. *Acta anaesthesiologica Scandinavica*. 2017; **61**: 914–924.
15. Doyen D, Moschietto S, Squara F, Moceri P, Hyvernat H, Ferrari E, Dellamonica J, Bernardin G. Incidence, clinical features and outcome of Takotsubo syndrome in the intensive care unit. *Arch Cardiovasc Dis*. 2020; **113**: 176–188.
16. Ruiz Bailén M, Aguayo de Hoyos E, López Martnez A, Daz Castellanos MA, Ruiz Navarro S, Fierro Rosón LJ, Gómez Jiménez FJ, Issa-Masad Khozouz Z. Reversible myocardial dysfunction, a possible complication in critically ill patients without heart disease. *J Crit Care*. 2003; **18**: 245–252.
17. Park JH, Kang SJ, Song JK, Kim HK, Lim CM, Kang DH, Koh Y. Left ventricular apical ballooning due to severe physical stress in patients admitted to the medical ICU. *Chest*. 2005; **128**: 296–302.
18. Bossone E, DiGiovine B, Watts S, Marcovitz PA, Carey L, Watts C, Armstrong WF. Range and prevalence of cardiac abnormalities in patients hospitalized in a medical ICU. *Chest*. 2002; **122**: 1370–1376.
19. Marcelino PA, Marum SM, Fernandes AP, Germano N, Lopes MG. Routine transthoracic echocardiography in a general Intensive Care Unit: an 18 month survey in 704 patients. *Eur J Int Med*. 2009; **20**: e37–e42.
20. Tavakol M, Ashraf S, Brener SJ. Risks and complications of coronary angiography: a comprehensive review. *Glob J Health Sci*. 2012; **4**: 65–93.
21. Metnitz PG, Moreno RP, Almeida E, Jordan B, Bauer P, Campos RA, Iapichino G, Edbrooke D, Capuzzo M, Le Gall JR, Investigators S. SAPS 3--From evaluation of the patient to evaluation of the intensive care unit. Part 1: Objectives, methods and cohort description. *Int Care Med*. 2005; **31**: 1336–1344.
22. Moreno R, Vincent JL, Matos R, Mendonça A, Cantraine F, Thijs L, Takala J, Sprung C, Antonelli M, Bruining H, Willatts S. The use of maximum SOFA score to quantify organ dysfunction/failure in intensive care. Results of a prospective, multicentre study. Working Group on Sepsis related Problems of the ESICM. *Int Care Med*. 1999;**25**:686-696.
23. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, Hotchkiss RS, Levy MM, Marshall JC, Martin GS, Opal SM, Rubenfeld GD, van der Poll T, Vincent JL, Angus DC. The third international consensus definitions for sepsis and septic shock (sepsis-3). *JAMA*. 2016; **315**: 801–810.
24. Evangelista A, Flachskampf F, Lancellotti P, Badano L, Aguilar R, Monaghan M, Zamorano J, Nihoyannopoulos P, European Association of E. European Association of Echocardiography recommendations for standardization of performance, digital storage and reporting of echocardiographic studies. *Eur J Echocardiogr*. 2008; **9**: 438–448.
25. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2015; **28**: 1–39 e14.
26. Stanko LK, Jacobsohn E, Tam JW, De Wet CJ, Avidan M. Transthoracic echocardiography: impact on diagnosis and management in tertiary care intensive care units. *Anaesth Intensive Care* 2005; **33**: 492–496.
27. Picard MH, Wilkins GT, Ray P, Weyman AE. Long-term effects of acute thrombolytic therapy on ventricular size and function. *Am Heart J*. 1993; **126**: 1–10.
28. Rowell AC, Stedman WG, Janin PF, Diel N, Ward MR, Kay SM, Delaney A, Figtree GA. Silent left ventricular apical ballooning and Takotsubo cardiomyopathy in an Australian intensive care unit. *ESC Heart Fail*. 2019; **6**: 1262–1265.
29. Ghadri JR, Cammann VL, Napp LC, Jurisic S, Diekmann J, Bataiosu DR, Seifert B, Jaguszewski M, Sarcon A, Neumann CA, Geyer V, Prasad A, Bax JJ, Ruschitzka F, Luscher TF, Templin C. Differences in the clinical profile and outcomes of typical and atypical Takotsubo syndrome: data from the International Takotsubo Registry. *JAMA Cardiol*. 2016; **1**: 335–340.
30. Isogai T, Yasunaga H, Matsui H, Tanaka H, Ueda T, Horiguchi H, Fushimi K. Out-of-hospital versus in-hospital Takotsubo cardiomyopathy: analysis of 3719 patients in the Diagnosis Procedure Combination database in Japan. *Int J Cardiol*. 2014; **176**: 413–417.
31. Ghadri JR, Wittstein IS, Prasad A, Sharkey S, Dote K, Akashi YJ, Cammann VL, Crea F, Galiuto L, Desmet W, Yoshida T, Manfredini R, Eitel I, Kosuge M, Nef HM, Deshmukh A, Lerman A, Bossone E, Citro R, Ueyama T, Corrado D, Kurisu S, Ruschitzka F, Winchester D, Lyon AR, Omerovic E, Bax JJ, Meimoun P, Tarantini G, Rihal CSYH, Migliore F, Horowitz JD, Shimokawa H, Luscher TF, Templin C. International expert consensus document on Takotsubo Syndrome (Part I): clinical characteristics, diagnostic criteria, and pathophysiology. *Eur Heart J*. 2018; **39**: 2032–2046.
32. D'Andrea A, Radmilovic J, Mele D, D'Ascenzi F, Agricola E, Carbone A, Lo Iudice F, Novo G, Ancona F, Righini FM, Mondillo S, Bossone E, Galderisi M, Working Group on Echocardiography of the Italian Society of C. Speckle tracking analysis in intensive care unit: A toy or a tool? *Echocardiography*. 2018; **35**: 506–519.
33. Dalla K, Bech-Hanssen O, Oras J, Naredi S, Ricksten SE. Speckle tracking-vs conventional echocardiography for the detection of myocardial injury-A study on patients with subarachnoid haemorrhage. *Acta anaesthesiologica Scandinavica*. 2019; **63**: 365–372.