Lactate and other biomarkers as treatment target in cardiogenic shock

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Purpose of review
Cardiogenic shock remains beside sudden cardiac death the most outcome relevant complication of acute myocardial infarction. Over the last two decades as confirmation of the benefit of early revascularization no further relevant improvement in outcome could be achieved. Biomarkers are important for diagnosis, monitoring, and management in cardiogenic shock patients.

Recent findings
A bunch of different biomarkers have been associated with prognosis in patients with cardiogenic shock. In routine use standard parameters such as serum lactate or serum creatinine are still most important in monitoring these patients. These established markers outperformed novel markers in prognostic impact in recent trials.

Summary
Biomarkers serve as important treatment targets and may help physicians in therapeutic decision-making. Furthermore, the complex pathophysiology of cardiogenic shock may be better understood by investigation of different biomarkers.

Keywords
biomarkers, cardiogenic shock, myocardial infarction

INTRODUCTION

Acute myocardial infarction complicated by cardiogenic shock is – beside sudden cardiac death – the most feared and outcome relevant complication. In myocardial infarction without development of cardiogenic shock mortality rates declined significantly over the last two decades because of development of therapeutic, technical, as well as medical improvements. This has reduced the rates of patients developing cardiogenic shock in acute coronary syndromes after hospital admission [1,2]. In contrast, more patients already in cardiogenic shock are transferred by emergency medical systems to the hospital [2,3]. This fact is maybe evident because of a change in prehospital triage, bringing sicker patients to hospital instead of letting them pass away at home. When comparing long-term outcome of patients in cardiogenic shock included in the intraaortic balloon pump in cardiogenic SHOCK (IABP-SHOCK) II-trial (patient inclusion from 2009 to 2012) to patients randomized in the early revascularization arm of the SHOuld we emergently revascularize occluded coronaries for cardiogenic shoCK (SHOCK) trial (patient inclusion from 1993 to 1998) no differences could be observed [4,5]. Recent registry data in an overall cardiogenic shock population (at admission and development during hospitalization) showed a slight reduction in mortality over a 20-year period. This is possibly related to an increase of early revascularization from 40% (period 1997–2006) to 80% (period 2007–2017) [2]. Crucial is the early recognition of cardiogenic shock and to detect changes in patient's status pointing either to stabilization or to aggravation of cardiogenic shock. Biomarkers, especially serum lactate, are important diagnostic tools to assess the overall status as well as recognition of organ failure. Furthermore, our understanding of pathophysiology of cardiogenic shock is still under progression as this condition reflects a systemic illness in reaction to general end-organ hypoperfusion [6]. Investigation of biomarkers is therefore important for further

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KEY POINTS

- Arterial lactate is important for diagnosis of cardiogenic shock and monitoring patients.
- Routine biomarkers for end-organ failure may provide better prognostic information than novel more sensitive parameters.
- Biomarkers help us to understand the complex pathophysiology of cardiogenic shock.

understanding of possible pathophysiological pathways.

DEFINITION AND DIAGNOSIS OF CARDIOGENIC SHOCK

Cardiogenic shock is defined as a state of critical end-organ hypoperfusion because of primary cardiac dysfunction [7,8▪▪]. The diagnosis of cardiogenic shock is primarily based on clinical parameters including hypotension (i.e., systolic blood pressure <90 mmHg, or need for catecholamine support to achieve a blood pressure ≥90 mmHg), and signs of impaired organ perfusion such as central nervous system abnormalities including confusion or lack of alertness, or even loss of consciousness; oliguria; cold, clammy skin, and extremities, increased arterial lactate more than 2 mmol/l in the state of normo or hypervolemia. As clinical factors may be misinterpreted, arterial lactate plays a key role in diagnosis of cardiogenic shock. Nowadays lactate is widely and with point of care testing immediately available in emergency departments and intensive care units. In actual sepsis guidelines, the definition of shock is based solely on low blood pressure (need for vasopressor therapy to maintain a mean arterial blood pressure ≥65 mmHg and elevated serum lactate >2 mmol/l) [9]. In contrast for cardiogenic shock, dedicated international guidelines are still missing and therefore no consensus on exact definition exists [8▪▪].

SYSTEMIC PARAMETERS

Early prognostication has become a major issue in the last years. Clear data to guide therapy especially for escalation to mechanical assist devices are lacking. Yet, the use of these devices in an overall shock population is not recommended [7]. Therefore, efforts have been taken to define a high-risk population in early shock phase and different scores have been published [10,11]. Biomarkers have been incorporated in both scores (Table 1). In the CardShock risk score arterial lactate and kidney function by estimated glomerular filtration rate is used. The IABP-SHOCK II risk score uses also lactate levels and kidney function and blood glucose levels.

Arterial lactate for prognostication

The prognostic value of lactate in cardiogenic shock has been proven in several studies performed in the last decades [12,13]. In septic shock single lactate values and also decline over time, the lactate clearance, has been introduced as important marker [14]. In a large cohort of 2191 critically ill patients, the delta of arterial lactate levels between day 1 and 2 showed an independent association to adverse outcome [15]. In cardiogenic shock only little data exist for lactate clearance [16]. For patients undergoing

Table 1. Scores for early prognostication in cardiogenic shock

	CardShock Risk Score		IABP-SHOCK II Risk Score	
	Variable	Points	Variable	Points
Clinical	Age >75 years	1	Age >73 years	1
	Confusion at presentation	1	History of stroke	2
	Previous MI or CABG	1	TIMI flow grade <3 after PCI	2
	ACS cause	1		
	LVEF <40%	1		
Biomarkers	Arterial lactate <2 mmol/l 2–4 mmol/l >4 mmol/l	0 1 2	Arterial lactate >5 mmol/l	2
	$eGFR_{CKD-EPI}$			
	>60 ml/min/1.73 m^2 30–60 ml/min/1.73 m^2 <30 ml/min/1.73 m^2	0 1 2	Creatinine >132.6 μmol/l	1
			Glucose >10.6 mmol/l	1
Maximum points		9		9

ACS, acute coronary syndrome; CABG, coronary angiography bypass grafting; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MI, myocardial infarction; TIMI, thrombolysis in myocardial infarction.

mechanical extracorporeal life support in cardiogenic shock, a recent study found that lactate values before insertion of the device and also peak levels did not show a significant association to outcome [17▪]. In contrast, single lactate and lactate clearance after 24 h were good predictors of 30-day mortality. Yet, data investigating arterial lactate clearance in a large cohort powered to detect relevant differences in outcome is missing. Lactate itself may act as alternative energy supply in shock patients. At rest, most cardiac energy is gained by β-oxidation of fatty acids and pyruvate [18], whereas during exercise or other stress situations lactate seems to be an important source of energy [19]. The uptake of lactate into the heart increases [20,21]. Possibly high lactate levels reflect a stress response of the body with activation of the sympathetic nervous system, increased glycolysis, and a modified bioenergetic supply in shock patients [22].

Blood glucose levels and outcome in cardiogenic shock

In the past years, different studies investigated the prognostic role of blood glucose levels in cardiogenic shock. A small study found variability in blood glucose levels over the first 48 h to be predictive of mortality [23]. A secondary analysis of the CardShock Study in 211 patients showed that patients with severe hyper or hypoglycemia are at highest risk for mortality. Yet, with only five patients in the hypoglycemic group these findings for low glucose levels warrant confirmation in a larger cohort. The largest investigation to date is a sub-analysis of the IABP-SHOCK II-trial in 513 patients with available baseline glucose levels [24▪▪]. Of these, 33.7% had known diabetes. Notably the predictive ability of baseline glucose levels was independent from the absence or presence of diabetes.

Growth differentiation factor 15

The growth differentiation factor 15 (GDF-15), a transforming growth factor β-cytokine, has shown prognostic impact in several cardiac conditions [25]. In acute non-ST-elevation acute coronary syndromes [26] and ST-elevation myocardial infarctions [27] without cardiogenic shock GDF-15 levels were a strong predictor of survival. In patients with myocardial infarction complicated by cardiogenic shock this association has also been found in a substudy of the IABP-SHOCK II-trial [28]. Furthermore, in cardiogenic shock GDF-15 levels (median 7662 ng/l, [28]) were found to be elevated over that reported in hemodynamic stable myocardial infarctions (median 1443 ng/l, in ST-elevation myocardial infarction [27] and 1152 ng/l in non-ST-elevation acute coronary syndromes [26]). Comparable levels to cardiogenic shock patients were found in patients with end-stage chronic heart failure (mean 7100 ng/l [29]), notably with a significant decline to nearly normal values after implantation of left ventricular assist devices. The prognostic impact of baseline GDF-15 in cardiogenic shock was independent from arterial lactate and the combination of GDF-15 and lactate showed a significant improvement of prognostic prediction in short-term mortality using c-statistics [28]. GDF-15 remained also significantly associated with mortality after multivariable adjustment including N-terminal brain natriuretic peptide (NT-proBNP). NT-proBNP – routinely used a prognostic marker in heart failure – was not associated with short-term mortality in multivariable analysis [28]. However, studies with serial measurements of GDF-15 in cardiogenic shock and comparison to arterial lactate in monitoring treatment success are lacking.

BIOMARKERS ASSOCIATED WITH END-ORGAN FAILURE

The development of multiorgan dysfunction has a major impact on prognosis in cardiogenic shock [30,31▪]. Biomarker sampling although not investigated prospectively is recommended in cardiogenic shock patients [32]. Therefore, early recognition of loss of function of single organs may be useful to assess prognosis and possibly for treatment decisions.

Kidney parameters in cardiogenic shock

Acute renal failure is common in cardiogenic shock. Accordingly, low urine output is an optional diagnostic criterion reflecting systemic hypoperfusion in cardiogenic shock [8▪▪]. Acute kidney failure has also shown strong prognostic impact in these patients [33] and was also used as part of the combined primary endpoint in the recently published Culprit Lesion Only PCI Versus Multivessel PCI in Cardiogenic Shock (CULPRIT-SHOCK) trial [34–36]. Interestingly, in these high-risk patients common serum creatinine outperformed novel biomarkers such as cystatin C, neutrophil gelatinase-associated lipocalin, and kidney injury molecule-1 for renal function in prediction of 1-year outcome [33].

Fibroblast growth factor-23

Another interesting biomarker connected with kidney function is bone-derived fibroblast growth factor-23 (FGF-23). The effects on phosphate regulation and vitamin D metabolism depend on

its interaction together with the obligatory renal co-receptor α-klotho interaction with renal tubular cells [37]. In cardiogenic shock, FGF-23 is elevated and showed a significant association to mortality [38]. This association has been confirmed in another larger cardiogenic shock study [39]. Further studies must clarify whether FGF-23 is just an innocent bystander being upregulated because of the impaired kidney function and left ventricular dysfunction or is an independent player itself.

Liver failure in cardiogenic shock

In cardiogenic shock, liver failure – also known as hypoxic hepatitis – is triggered by arterial hypoperfusion as well as venous congestion. It is characterized by centrilobular liver cell necrosis and distinctly elevated serum aminotransferase levels. In a recently published substudy of the IABP-SHOCK II-trial 18% of patients had hypoxic hepatitis [40▪▪]. These patients had 2.5-fold higher 30-day mortality than patients without acute liver failure. Similarly, to acute kidney failure in cardiogenic shock, novel markers such as argininosuccinate synthase 1 and sulfotransferase isoform SULT2A1 failed to outperform the common markers in prediction of short-term prognosis.

Intestinal perfusion

The intestinal tract is one of the largest organs of the human body and requires up to 30% of the cardiac output of a healthy person. Therefore, an impaired perfusion because of low output and increased systemic vascular resistance possibly aggravated by the use of vasopressors may cause hypoxic epithelial injury and a consecutive inflammatory response with possible transmigration of bacteria into the circulation [41]. The intestinal fatty acid binding protein (iFABP), specifically located in small bowel enterocytes is liberated into the circulation upon intestinal epithelial injury. A small study in 90 patients with cardiogenic shock or severe acute heart failure was able to show an independent association of baseline high iFABP levels with mortality [42▪▪]. Interestingly, this association was no more evident at day 3.

Blood vessels and endothelium

Cardiogenic shock may also impact blood vessels including microcirculatory dysfunction, vascular leakage with edema formation, and may lead to an increase in platelet and leukocyte adhesion to the endothelium. The inner layer of the endothelium, a mesh of proteoglycans, glycosaminoglycans, and glycoproteins, the so-called glycocalyx is a central modulator of these processes [43]. In a recent large cohort study including patients with ST-elevation myocardial infarction, those patients with cardiogenic shock had higher glycocalyx levels in comparison to patients without cardiogenic shock [44]. This investigation could also confirm the prior shown association of high glycocalyx levels on mortality in cardiogenic shock patients [44,45]. A sub-analysis of the IABP-SHOCK II-trial patients randomized to IABP had no differences in syndecan-1 levels as marker of the glycocalyx in comparison to control at baseline. However, IABP-treated patients had significantly higher levels at day 2. This implicates some interaction of the IABP with the endothelium of the aorta [45].

BIOMARKERS ASSOCIATED WITH INFLAMMATION

Over the last two decades, a paradigm change has been postulated expanding pathophysiology in cardiogenic shock from a simple low output syndrome to a more complex syndrome involving inflammation and nitric oxide production [46]. Nowadays the well-accepted pathophysiological concept in cardiogenic shock includes an activation of a systemic inflammatory response [8▪▪]. Classical inflammatory markers such as interleukins have been associated with mortality in these patients [47,48]. Currently, no studies have tested anti-inflammatory pathways in cardiogenic shock. However, a large randomized trial to inhibit nitric oxide synthase failed to show any survival benefit and the study was terminated early for futility [49]. Therefore, our understanding of cardiogenic shock pathophysiology may get better in investigating further biomarkers linked to inflammation.

Angiopoietin-2

Angiopoietin-2 is an important mediator of capillary leakage as a reaction to systemic inflammation [50]. In cardiogenic shock nowadays it is well known that development of a systemic inflammatory response syndrome plays a key role in persistent cardiogenic shock [46]. Vascular barrier dysfunction plays an important negative prognostic role, initiating and perpetuating a vicious circle toward the development of multiorgan dysfunction syndrome. Angiopoietin-2 has been found to be significantly elevated in cardiogenic shock [51]. Furthermore, its prognostic impact has been shown in serial measurements also confirming a significant rise of angiopoietin-2 after complications such as bleeding [52].

Catalytic iron

Another possible player in the complex biochemical cascade in cardiogenic shock is catalytic iron. It is nontransferrin, nonferritin bound free circulating oxidized ferric iron, acts as a powerful catalyst for production of reactive oxygen species, and triggers the release of free hydroxyl radicals leading to vascular injury mediated by endothelial apoptosis [53,54]. A strong correlation to bleeding events has been found in cardiogenic shock patients possibly explaining one of the mechanisms bleeding complications can modify outcome. Furthermore, a strong correlation to prognosis could be observed in cardiogenic shock patients [55].

Selenoprotein P

Several antioxidative and immune regulatory processes depend on selenium which in large proportions is bound to circulating selenoprotein P (SelP). In cardiogenic shock, a recent published study found significantly higher values of SelP in patients with cardiogenic shock complicating acute myocardial infarction compared to healthy controls, although the univariable association to mortality did not remain significant after multivariable adjustment [56▪]. Furthermore, SelP levels showed a relative increase between day 1 and 3 in cardiogenic shock patients.

CONCLUSION

Biomarkers are important diagnostic and prognostic tools in cardiogenic shock patients (Table 2). Arterial lactate is part of the diagnostic strategy in cardiogenic shock and an important prognosticator. Furthermore, because of its fast availability by point-of-care testing it is also used as important monitoring parameter. Monitoring of end-organ function includes several routine biomarkers such as serum creatinine, which are regularly controlled in intensive care patients. Interestingly, long-established markers for kidney and liver function provide better prognostic information than more sensitive novel biomarkers. These parameters are used for therapeutic decisions and have high prognostic impact. Markers of inflammation are also of prognostic relevance yet not used in routine patient management.

Table 2. Overview of biomarkers in this review

	Biomarker	Prognostic impact	Routine marker	References
Systemic parameters				
	Arterial lactate	+++	+	[8▪▪,10–13,15,17▪]
	Blood glucose	+++	+	[23,24▪▪]
	N-terminal prohormone of brain natriuretic peptide	+	+	[28]
	Growth differentiation factor 15	+++	–	[28]
End-organ failure				
Kidney	Serum creatinine	+++	+	[33]
	Cystatin C	+/–	–	[33]
	Neutrophil gelatinase-associated lipocalin	+	–	[33]
	Kidney injury molecule-1	+/-	–	[33]
Kidney associated	Fibroblast growth factor-23	++	–	[38,39]
Liver	Alanine-aminotransferase	++	+	[40▪▪]
	Aspartate-aminotransferase	++	+	[40▪▪]
	Glutamate-dehydrogenase	+	+	[40▪▪]
	Sulfotransferase isoform SULT2A1	–	–	[40▪▪]
	Argininosuccinate synthase 1	–	–	[40▪▪]
Intestinal tract	Intestinal fatty acid binding protein	+	–	[42▪▪]
Blood vessels	Syndecan-1	++	–	[44,45]
Biomarkers associated with inflammation			–	
	Angiopoietin-2	++	–	[51,52]
	Catalytic iron	++	–	[55]
	Selenoprotein P	+	–	[56▪]

Used in clinical trials these markers give us further information on pathophysiology in cardiogenic shock and some may have the potential for a therapeutic target in future.

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Conflicts of interest

There are no conflicts of interest.

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