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Review Article

The Cardiovascular Effects of Hypertonic Lactate: A Systematic Review of Animal Studies

Hørsdal OK, MS[1,2*]

[1]Department of Clinical Medicine, Aarhus University, Denmark

[2]Department of Cardiology, Aarhus University Hospital, Denmark

***Corresponding author:** **Oskar K Hørsdal**

Department of Clinical Medicine, Aarhus University, Denmark.

Tel: +45 27 82 81 02

Email: osho@clin.au.dk

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Abstract

The naturally occurring metabolite lactate has traditionally been considered as a waste product of anaerobic metabolism whose production was confined to hypoxic states. However, more evidence supports that lactate is a preferred oxidative substrate for stressed myocardium. Small scale clinical studies have found that infusion of exogenous Hypertonic Sodium Lactate (HSL) increases cardiac output and stabilizes the haemodynamic profile. More comprehensive studies investigating haemodynamic or cardiovascular effects of HSL have been conducted using different animal models of disease.

We performed a broad systematic search of electronic databases PubMed and Embase to identify animal studies in which haemodynamic or cardiovascular effects of HSL were reported. A total of 133 studies were identified. 17 studies were included in this review. Different disease models were included including sepsis (n=4 studies), cardiac arrest (n=3 studies), myocardial infarction (n=2 studies), haemorrhagic shock (n=3 studies) while studies on healthy hearts (n=2 studies) were included. Also 3 studies investigating the cardioprotective and cardiometabolic roles of HSL were included.

The review revealed several beneficial haemodynamic effects of HSL infusion during a variety of disease state including increased cardiac output, increased microcirculation, and decreased inflammation. Only few studies identified negative effects of HSL infusion. This paper concludes that high doses of lactate serve the potential as an important cardiac fuel during crisis situations. However, the review revealed significant flaws in the reporting quality of majority of studies. Future translational studies should focus on enhancing reproducibility, study design and study reporting.

Keywords: Metabolism; Lactate; Inflammation; Shock; Cardiovascular; Animal studies

Abbreviations: CPR: Cardiopulmonary Resuscitation; CO: Cardiac Output; ECG: Electrocardiographic; HSL: Hypertonic Sodium Lactate; HSB: Hypertonic Sodium Bicarbonate; HS: Hypertonic Saline; MAP: Mean Arterial Blood Pressure; MB: Methylene Blue; NS: Normotonic Saline; PCWP: Pulmonary Capillary Wedge Pressure; P(v-a)CO2: Venoarterial CO2 difference; RL: Ringer's Lactate; ROSC: Return of Spontaneous Circulation

Introduction

The traditional view of lactate as a by-product of anaerobic metabolism during hypoxia has led to its reputation as a worthless or potentially harmful substance [1]. Often blood levels of lactate are used to evaluate the severity of illness [2-4]. However, the disease states leading to lactate accumulation, rather than lactate *per se,* is to blame. In fact, myocardial lactate deprivation is associated with earlier death and worsened outcome during endotoxic and haemorrhagic shock [5,6]. Also, current research compellingly indicates that lactate production is not exclusive to anaerobic conditions but also occurs during fully aerobic circumstances, even in resting state [7-9] suggesting that lactate production is a fundamental physiological process that occurs in both health and disease.

The healthy heart exhibits metabolic versatility, capable of utilizing various substrates such as free fatty acids, glucose,

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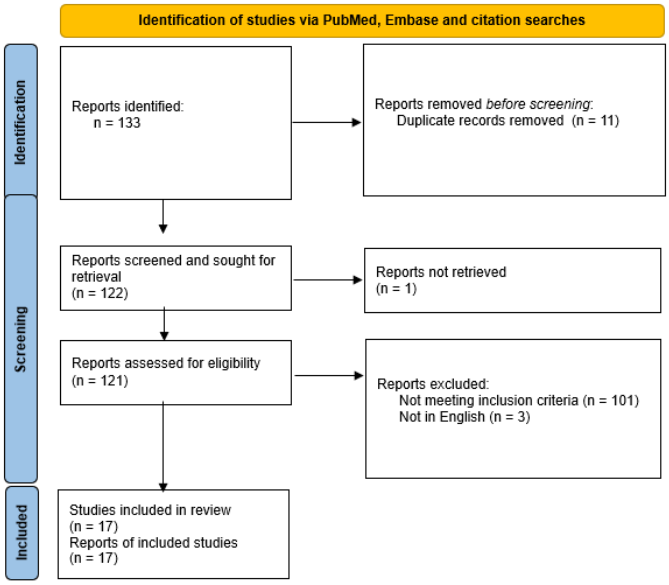

Figure 1: PRISMA diagram

ketone bodies, lactate, and amino acids, with a preference for free fatty acids under normal conditions [10,11]. Recent studies have highlighted lactate as a promising fuel source that can significantly enhance cardiac function in patients with heart failure [12] and during exercise [13]. Furthermore, increased myocardial lactate consumption during heart failure is associated with increased stroke volume and improved left ventricle efficiency [14].

Table 1: Search string.
The original search was performed in May 2023. The final search strategy was

In title or abstract		In title or abstract		Mesh term
Haemodynamic* OR Hemodynamic OR Cardiovascular OR Cardiac*	AND	"Lactate infusion" OR "Exogenous lactate" OR "Sodium lactate"	AND	Animal

Due to the unjustified negative repute of lactate research in the topic have not been considered very appealing, though highly relevant. Therefore, only a limited number of studies have been conducted to determine its precise haemodynamic and cardiovascular effects and its potential as a treatment option. Historically, small-scale clinical trials involving human patients have been conducted on patients after cardiac arrest and during atrioventricular block [15] and cardiac arrhythmias during cardiac surgery [16]. More recently studies have been done on healthy volunteers [17], patients with acute heart failure [12] and patients during or after cardiac surgery [18-20]. All studies report beneficial effects of hypertonic lactate infusion on cardiac haemodynamics. Still fascinating, these pioneering studies are relatively few and vary in terms of quality. More comprehensive translational trials utilizing different animal models and disease scenarios have been carried out.

This systematically performed review aimed to examine the existing evidence from animal studies to elucidate the cardiovascular and haemodynamic effects of exogenous hypertonic lactate infusion. The objective was to clarify the current understanding and shed light on knowledge gaps.

Table 2: Study characteristics and major findings.

	Country	Animal	Randomization	Blinding	Major findings	Ref
Sepsis (n=4)						
Duburcq et al 2014	France	Pigs	Yes	Not reported	- Stabilization of MAP in HSL group. - Better cardiac index in HSL group. - Lower venoarterial CO2 difference in HSL group.	23
Su et al 2016	Belgium	Sheep	Yes	Partly blinded*	- Lower MAP in HSL group - Lower cardiac index in HSL group. - Lower SvO2 in HSL group.	25
Duburcq et al 2017	France	Pigs	Yes	No	- Higher MAP and cardiac index in HSL group. - Higher SvO2 in HSL group - Lower venoarterial CO2 difference in HSL group. - Improved rectal microcirculation in HSL group.	24
Besnier et al 2020	France	Rats	Yes	Not reported	- Improved mesenteric perfusion in HSL group. - Increased LVEF in HSL group. - Higher cardiac output and ventricular shortening fraction in HSL group. - Higher dP/dt_{max} in HSL group. - Decreased inflammation in HSL group.	22
Cardiac arrest (n=3)						
Miclescu et al 2007	Sweden	Pigs	Yes	Not reported	- Lower CK-MB and troponin I in the methylene blue in HSL group.	28
Stevic et al 2002	France	Rabbits	Yes	Yes	- Higher MAP in the lactate group - Higher cardiac output in the lactate group - Higher left ventricle surface shortening fraction in the lactate group. - Lower EDP in the lactate group. - Decreased markers of brain injury in HSL group.	26
Annoni et al 2023	Belgium	Pigs	Yes	No	- Less norepinephrine required to maintain MAP>65 in HSL groups. - Lower levels of troponin I in HSL groups. - No difference in cardiac output. - Decreased markers of brain injury in HSL group.	27
Healthy hearts (n=2)						
Onay-Besikci 2007	Turkey	Rats	Not reported	Not reported	- Physiological concentration of lactate has no effect on cardiac function.	49
Barthelmes et al 2010	Switzerland	Pigs	Yes	Not reported	- Increased cardiac output in HSL groups. - Lower SvO_2 in HSL groups.	29

Myocardial infarction (n=2)						
Zhang et al 2021	China	Mice	Not reported	Not reported	- Enhanced ventricular fractional shortening in HSL group. - Enhanced LVEF in HSL group - Less myocardial fibrosis in HSL group	30
De Groot et al 1993		Rats				52
Haemorrhagic shock (n=3)						
Kline et al 2000	USA	Rats	Not reported	Not reported	- Improved cardiac efficiency in HSL group.	31
Rocha e Silva et al					- HSL-dextrane increased CO and MAP - HSL-dextrane reversed shock-induced acidosis - HSL-dextrane led to a higher cumulated blood loss	57
Schmoker et al 1991	USA	Pigs	Yes	No	- Increased cerebral oxygen delivery in HSL group	58
Cardioprotection (n=3)						
Haege et al 2021	USA	Zebrafish	Not relevant**	Not relevant**	- Activation of anti-inflammatory pathways - Decreased cardiac hypertrophy	32
Bellet et al 1959	USA	Dogs	No	No	- HSL diminished cardiotoxic effects of quinidine and procaine amide due to several mechanisms - HSL improved intoxication-induced hyperkaliemia and acidosis - HSL improved intoxication-induced hypotension and ECG alterations - HSL possible enacts as a readily oxidizable fuel for cardiomyocytes	64,65

*Blinding of operators was not done. Blood flow video data underwent blinded analyses. **Study was a drug discovery study. All animals were treated equally.
**Apart from basic haemodynami monitoring of heart rate and ECG.

Methods

Data Sources and Search Strategy

A scoping review was performed focusing on study designs of hypertonic lactate infusion in animal models. The PRISMA 2020 guidelines [21] were followed wherever possible.

We did a systematic search of the electronic PubMed and Embase databases for animal studies involving infusion of hypertonic exogenous lactate reporting haemodynamic or cardiovascular comes. Forward and backwards citation searches were performed for included trials.

We conducted a comprehensive search with high sensitivity using terms that encompassed our primary concepts of animal models receiving exogenous lactate infusion with a goal of raising blood levels of lactate. Only original studies that measured and reported on haemodynamic or cardiovascular endpoints and administered exogenous sodium lactate were included. We excluded all reviews, protocols, abstracts, studies not published in peer-reviewed journals and studies that did not involve animal models. The search string is shown in Table 1.

A total of 133 studies were identified. 11 duplicates were removed. 64 studies were removed due to not meeting the inclusion criteria (here of 3 studies not in English, and 1 study not found), 27 studies underwent full text analysis. 17 studies were included (see PRISMA diagram in Figure 1). A search for reporting of randomization and blinding was conducted in all included studies by using search terms *(random)* and *(blind)*.

Diseases

Lactate infusion have been tested in a variety of disease settings in animal models (Table 2). These include four studies of lactate infusion during septic- or endotoxic shock [22-25], three studies of lactate infusion as resuscitation fluid during or after cardiac arrest [26-28], two studies of lactate infusion in healthy animals [29], one study of lactate infusion in myocardial infarction [30], and one study involving isolated rat hearts after haemorrhagic shock [31]. Finally, one study was a drug discovery test involving an Acute Heart Failure (AHF) model [32].

Animals

Six of the included studies used large animal models (pig studies; n=5, sheep studies; n=1).

In the succeeding sections the following abbreviations for treatment options will be used: Hypertonic Sodium Lactate (HSL), Hypertonic Sodium Bicarbonate (HSB), Hypertonic Saline (HS) and Normotonic Saline (NS).

Results

Cardiovascular Effects During Sepsis (n=4 studies)

Study results: In 2020 Besnier et al. [22] used rats and induced shock by fecal peritonitis. They included four study groups. One control group and three sepsis groups. The sepsis groups received either Hypertonic Sodium Lactate (HSL), Normotonic Saline (NS) or Hypertonic Bicarbonate (HSB) with equivalent amounts of sodium and osmoles as HSL. Four of six of the first rats in HSB died, hence this group was not completed. The groups were observed for 18 hours. They found beneficial haemodynamic and cardiovascular effects during HSL as compared with NS including increased Cardiac Output (CO), left ventricular fractional shortening and dP/dt_{max}. They found no effect on end systolic pressure volume relationship therefore the dP/dt_{max} increase was likely due to preload- or afterload alterations. The group also found improved mesenteric microcirculation measured using laser speckle contrast imaging on the gut, lowered end-diastolic pressure-volume relationship and increased blood levels of the ketone body 3-OHB. Furthermore, they found HSL to decrease capillary leakage and reduce inflammation as they found a lower level of IL-1, TNF-alpha and VEGF-A. Finally, they found that HSL infusion led to a negative fluid balance.

In two independent studies Duburcq et al. [23,24] used pigs as animal model and utilized intravenous injection of E. coli endotoxin to induce hypodynamic shock. In 2014 they included three groups (n=5 in each) where one received HSL, one control group received NS and one group received HSB with equal amounts of osmoles and sodium as well as the same alkalizing effect as the hypertonic sodium lactate group. In 2017 Duburcq et al. repeated the study with the addition of 39 g of glucose

to the infusions in the HSB and NS groups to infuse equivalent energy supply as the SL group. In both studies the pigs were observed for 5 hours. In both studies Duburcq et al. found that HSL was superior to HSB and NS regarding haemodynamic effects. In 2014 the group found that cardiac index was less impaired by the endotoxic shock after 5 hours observation in the HSL group compared with NS (p=0.01) while they found no significant difference between HSL and HSB groups. They also found that Mean Arterial Blood Pressure (MAP) was significantly better in the HSL group compared with HSB and NS. They also found improved microvascular reactivity with lower venoarterial CO_2 tension (P(v-a) CO_2) difference in the HSL group compared with both HSB and NS. In 2017 the group, again, found significantly improved cardiac index in the HSL group, as well as improved MAP. Mixed venous saturation (SvO_2) and P(v-a) CO_2 were also were improved in the HSL group. The authors found this to compliment the finding of higher CO and improved peripheral perfusion. Finally, the group found that HSL led to a negative fluid balance measured as fluid infusion volume vs urine output.

In 2016 Su et al. [25] used sheep and induced hyperdynamic shock by fecal peritonitis. They included a HSL group, a Hypertonic Saline (HS) group, a NS and a Ringer's Lactate (RL) group in their study. The sheep were observed until spontaneous death. The group found decreased cardiac index in the HSL group compared with the HS group after 12 and 16 hours. Also, they found more severe microcirculatory alterations in the HSL group. The same was true for the renal blood flow, again indicating low CO and end organ hypoperfusion. Finally, the survival time was shorter in the HSL group vs HS or RL group.

Discussion: Use of Lactate in Sepsis Treatment

Sepsis is associated with profound deficit in effective blood volume due to vasodilation and capillary leakage. Therefore, large amounts of intravenously infused fluids are often used aiming to restore volume status, CO, and organ perfusion. This however often happens at the expense of tissue oedema formation that may influence organ function [33-35]. Low volumes of hypertonic fluids could therefore have beneficial effects. However, the high concentrations of chloride may lead to kidney injury [36,37]. The evidence from animal studies investigating effects of exogenous HSL infusion for sepsis in the present review, though limited to four studies, indicates that HSL infusion could prevent tissue oedema or chloride-induced kidney injury as three studies found that HSL led to negative fluid balance and HSL contains less chloride than HS.

The fact that high lactate levels during sepsis could be beneficial is supported by data provided by a study from 2007 that used live rats undergoing endotoxic shock. The study reported that myocardial lactate deprivation was associated with decreased cardiovascular performance and energetics as well as early death [5].

The large animal studies done by Su et al. [25] and Duburcq et al. [23,24] found somewhat opposing results. In the comparison of these studies several factors should be considered. First, Su et al. used an ovine model while Duburcq et al. used pigs. This, however, should not have any influence on the results as both large animal models are capable of mimicking human physiology and thoracial anatomy [38-40]. Secondly, both groups used randomization for treatment allocation while only Su et al. reported blinding of data analysis. Blinding generally enhances the validity of the results. Thirdly, one remarkable difference between the studies was the amount of lactate infused. While Su et al. only infused 200 mmol during a 15-h period, Duburcq et al infused 450 mmol during a 4.5-h period, a total of more than seven times more lactate infused. Therefore, the infused amount of lactate by Su et al. may be insufficient. Finally, Duburcq argues that the HSL-group in the study by Su et al. was under-resuscitated and received 30% less volume than did the HS group. On the other hand, Su et al. claims that Duburcq 2014, uses a less clinically relevant model with fixed-dose fluid resuscitation. Though there remain some discrepancy between study results, most studies found that HSL led to a beneficial haemodynamic profile with improved MAP, CO, and improved organ perfusion. The exact mechanism of action remains unclear.

Future studies are needed to fully clarify the cardiovascular and haemodynamic effects of sodium lactate infusion. Especially, the effects of different doses, infusion rates and differences between dynamic- and fixe dose fluid regimes of HSL infusion during sepsis should be examined. Also, the exact cardiovascular mechanism of action of lactate needs to be investigated. Furthermore, quality of reporting should be improved. Though all four studies were randomized only two studies reported that they did not include blinding of operators while the remaining studies did not report on blinding.

Cardiovascular Effects During Cardiac Arrest (n=3 studies).

Study results: Miclescu et al. [28] used a pig model of cardiac arrest with 12 min of cardiac arrest and 8 min of Cardiopulmonary Rescucitation (CPR). Cardiac arrest was induced using alternating transthoracic current. Animals were studied for 4 hours. They tested three different treatment options during CPR, all including Methylene Blue (MB). The three options were MB in NS, MB in saline dextrane and MB in HSL in randomized order. Pigs receiving MB in HSL had lower levels of troponin I and CKMB than pigs receiving MB in NS indicating less myocardial damage. Also, the Pulmonary Capillary Wedge Pressure (PCWP) was increased in the MB in NS group after Return of Spontaneous Circulation (ROSC). They concluded that MB in HSL had similar effects as MB in saline dextrane and that MB in HSL had better cardioprotective effects than MB in NS. They found no difference in survival or markers of cerebral injury.

Stevic et al. [26] used a cardiac arrest model on rabbits in 2020. The study was randomized and blinded. Cardiac arrest was induced by the withdrawal of mechanical ventilation in paralyzed animals. After 12.5 minutes of untreated arrest CPR was initiated until ROSC. The animals were studied for 2 hours. After stabilization rabbits would receive either continuous infusion of NS or HSL for 120 minutes. After 120 min HSL had significantly improved MAP, ventricular shortening fraction and CO as compared with NS. Also, the LV end diastolic pressure, the filling pressure, was lower in the HSL group (p=0.003). The diuresis was higher in the MSL group (p=0.014) and resulted in a neutral fluid balance. Finally, they found that HSL had a neuroprotective effect. They found no difference in survival.

Annoni et al. 2023 [27] used a pacing wire to induce cardiac arrest in a pig model. The study was randomized. After 10 min of cardiac arrest chest compressions were provided for 5 minutes before the first biphasic electric countershock. Epinephrine was administered after 1 min of cardiac arrest. Epinephrine and electric shock were provided every minute if ROSC was not present after the first round. Resuscitated animals were observed for 12 hours. The group randomized the pigs to receive either bolus NS followed by continuous infusion of balanced crystal-

loid, bolus HSL followed by continuous infusion of HSL or bolus NS followed by continuous infusion of HSL. The group found that significantly lower doses of norepinephrine was required to maintain a MAP >65 in both HSL groups compared with the NS group. The group also found that circulating levels of troponin I was lower in the HSL groups compared with NS group. They also found lower levels of markers of cerebral damage in the HSL groups. They found no difference regarding CO, PCWP, or other haemodynamic parameters. They found no difference in survival.

Discussion: Use of Lactate in Treatment of Cardiac Arrest

The cardiac arrest studies included in this review all find HSL infusion to result in a more beneficial haemodynamic profile if given during or after CPR compared with control. Small scale clinical studies conducted in 1955 also found HSL to be beneficial in treatment of cardiac arrest [15]. However, the studies are not without limitations. First, while all studies were randomized only Stevic et al. performed a blinded study. Annoni et al. reported that blinding of operators was not feasible while analysis of electroencephalographic data was performed blinded. Miclescu et al. did not report any blinding. Secondly, only Miclescu et al. used hypertonic fluid as a control fluid. Also, all of the used models of cardiac arrest are devoted to achieve the highest degree of ROSC, while still having a sufficient no-flow time to induce cardiac- and brain damage. Furthermore, the animals used were otherwise young and healthy and had no comorbidities. This contrasts with most cardiac arrest patients that are older and often display several comorbidities which can influence the cardiac arrest pathophysiology and treatment [41-43]. Therefore, many cardiac arrest models fail to replicate the severity of human cardiac arrest and is often of limited translatability to the clinical setting [44]. Additionally, the models used in this study only studies the animals for 2 to 12 hours, hence the lasting effects of cardiac arrest and treatment HSL have yet to be elucidated.

In the future studies could benefit from a design that more closely mimic human cardiac arrest [45]. Also, the studies could use hypertonic control fluids to account for the increased tonicity of HSL and the thereby following haemodynamic effects which include increased CO [18,46,47]. Additionally, optimal infusion regime and dose of HSL should be clarified. Furthermore, to shed a light on the longer lasting effects, the observation period of included animals should be extended. Finally, reporting quality should be improved. Though, all three studies were randomized, only two of three studies reported on blinding. One of these two studies reported that the study design involved blinding.

Despite the limitations, the positive effects of HSL in these innovative studies cannot be ignored: improved MAP, improved CO, decreased markers of cardiac injury, decreased markers of brain injury and less need for norepinephrine during resuscitation. Though these findings were not all reproduced across all studies, they are still of great interest and HSL should be further investigated as a resuscitation fluid.

Effects of Lactate on Healthy Hearts (n=3 studies)

Study results: In 2010 Barthelmes et al. [29] addressed the haemodynamic effects of HSL infusion in healthy pigs during central venous and portal vein administration of HSL. Pigs were randomly allocated to receive HSL in either a central vein, the portal vein, or a NS infusion. Animals were studied for 80 minutes of infusion and for 60 minutes post infusion. They found that pigs allocated to one of the HSL group had a significantly greater CO than did the NS group. HSL was administered at rates of 1, 2, 3, and 4 ml/kg/h for 20 minutes at each step. NS infusions were at the same rates. They found that HSL groups had an increased CO than did the NS group. They also found increased blood flow of hepatic and femoral arteries during HSL infusion. Interestingly, they also found that HSL groups had a lower arterial- and mixed venous oxygen saturation in the hour following the infusions.

In 1957 Bellet al. [48] examined the effects of lactate infusion in healthy dogs. The group found that infusion of 1 molar HSL at a rate of 0.5 ml/kg/min increased the CO without altering MAP. If, however, infused at doses of more than 0.5 ml/kg/min the group found depressed MAP, decreased force of myocardial contraction and electrocardiographic (ECG) changes consistent with infusion induced hypopotassemia. Onay-Besikci, 2007 [49] demonstrated that physiological levels of 1 mM lactate in the perfusion solution on healthy rat hearts, had no effect on cardiac parameters including heart rate, CO, MAP and aortic output.

Discussion: Haemodynamic Effects of Lactate in Healthy Animals

Interestingly, the only study involving a healthy large animal model, finds self-contradictory results. On one hand, the authors found that CO increased during HSL infusion. On the other hand, the authors claim that HSL infusion led to decreased SvO_2, a surrogate measure of perfusion and CO [50]. There may, however, be an explanation for this observation. Although the study protocol by Barthelmes et al. specified that pigs should be ventilated to maintain a PaO2 level above 13.3 kPa, this was not uniformly followed across all groups. Only the NS group adhered to the ventilation protocol, while the HSL groups were allowed to reach PaO2 levels as low as 8.5 kPa, resulting in arterial oxygen saturations of 91%. Consequently, the decline in SvO2 may potentially be attributed to inadequate ventilation rather than reflecting changes in CO. Unfortunately, the authors did not provide detailed information on the specific ventilator settings, making it impossible to delve further into the ventilation differences between the groups. Supporting the theory that HSL infusion increases CO in healthy animals Bellet et al. found that HSL infused in non-toxic doses increased CO and did not compromise MAP. In a separate study involving healthy hearts, Onay-Besciki found that addition of physiological amounts of lactate had no effects of cardiac function in isolated rat hearts. These findings indicate the presence of a therapeutic interval in which lactate has positive effect on the CO. Levels above or below this interval levels either compromises cardiac function or has no effect whatsoever.

In conclusion, in recent time only one study on healthy large animals have been conducted. Future randomized blinded studies are needed to investigate the haemodynamic effects of HSL in the healthy heart. These studies should ensure proper maintenance of ventilator settings to guarantee adequate comparability among groups with respect to oxygenation parameters. Also, studies should try to determine the therapeutic interval levels in which lactate has beneficial effects on cardiac and cardiovascular function. Finally, there is room for improvement regarding the reporting quality. Onay-Besciki's study lacked both reporting of randomization and blinding, while the study by Barthelmes et al. was randomized but lacked reported information on blinding. The study by Bellet et al. also lacked the reporting quality of modern standard.

Study results: In 2019 Zhang et al. [30] permanently ligated the Left Anterior Descending artery (LAD) inducing a Myocardial Infarction (MI) in a mouse model. The mice were injected with HSL or NS one day after surgery and consecutively for 14 days. After 14 days the mice were investigated with echocardiography. They found that HSL attenuated post-MI dysfunction by improving Ejection Fraction (EF) and ventricular fraction shortening. They concluded that HSL could improve cardiac function after MI. They also found significantly less myocardial fibrosis upon examination. Finally, they found HSL to enhance the expression of STAT-3 that is known to play multiple protective roles in the heart [51] possibly leading to anti-inflammatory polarization of macrophages. The study does not report on randomization nor blinding.

A 1993 study by de Groot et al. [52] investigated the effects of exogenous lactate, glucose, and pyruvate in the perfusion fluid of isolated rat hearts after 15, 30 and 45 minutes of ischemia on coronary flow. The study found that while the flow of the inner layers of the LV were reduced in lactate perfused hearts the flow in the outer layers were improved. Also, the relative flow in the right ventricle was increased.

Discussion: Use of Lactate During Myocardial Infarction

Only one study has investigated the effect of HSL treatment in a situation of *in vivo* MI. Hence, the need for more studies to ensure reproducibility appears obvious. Also, the included study did not use a control infusion of equal tonicity and therefore did not account for possible effects of hypertonicity. Despite these limitations, mouse models play pivotal roles in research of MI as they express similarity in many genes with humans as well as overall anatomical similarities [53,54]. Also at the chronic stage, the mouse heart remodels with systolic dysfunction as the human heart after MI [55]. Still, small animal models have some shortcomings compared with large animal models as pig or sheep. Large animal models share the similarities in size, anatomy and physiology of the human heart and thorax as well as a more complex immune system. Therefore, making predictions of human responses to therapies are more approachable if large animal models are used [38,56]. In the future, *in vivo* studies should make sure to compare HSL treatment for MI against another hypertonic fluid to diminish the effects of hypertonicity. Also, future studies could benefit from using larger animal models to make the results more clinically relevant. Again, reporting quality should be improved. The included study reported neither on randomization nor blinding.

Effects of Lactate in Haemorrhagic shock (n=3 studies)

Study results: In 2000 Kline et al. [31] used a model of haemorrhagic shock utilizing rats which were bled out in order to investigate the effects of lactate in the perfusion solution. They randomized the hearts to either of the following groups of solution: i) glucose only, ii) glucose and palmitate, iii) glucose and palmitate and lactate, iv) glucose and high palmitate or v) glucose and high palmitate and lactate. The main cardiovascular findings by the group were that the addition of 8.0 mM lactate significantly improved cardiac work in shocked hearts and increased cardiac efficiency. They concluded that lactate could improve rather than deteriorate cardiac energy metabolism after haemorrhagic shock.

A 1993 study from Rocha e Silva et al. [57] tested hypertonic sodium dextran against other hypertonic sodium dextran solutions: hypertonic sodium acetate dextran, and HSL-Dextrane (HSLD) in a dog model of uninterrupted arterial bleeding. 80 17 kg dogs were included. The study found that HSLD increased cardiac index measured by thermodilution and MAP compared to all other groups. HSLD also reversed shock induced acidosis. The group concluded that an increase in CO and MAP, however, led to a higher cumulated blood loss.

In 1991 Schmoker et al. [58] studied early and late effects of HSL in a pig model of haemorrhagic shock after bleeding the animals to a MAP of 50 mmHg. Animals were randomized to receive either HSL or RL as a bolus followed by continuous infusion. The group found no difference in CO or MAP during a 24 hour follow up period, but cerebral oxygen delivery increased in the HSL group as Intracranial Pressure (ICP) was reduced. The group concluded that the ICP reduction was due to cerebral dehydration due to the hyperosmolar composition of the HSL fluid ultimately leading to the increased cerebral blood blow and oxygen delivery.

Discussion: Use of Lactate During Haemorrhagic Shock

Though infusion of HSL led to higher cumulated blood loss in the study by Rocha e Silva et al. this is most likely a side effect to the increased CO and MAP found by the group. Despite this, HSL infusion seems a beneficial treatment for haemorrhagic shock if proper volume-replacement is being performed to account for increased blood loss due to several factors. First, restoration of circulation including improving MAP and CO is the most important thing during the acute management of haemorrhagic shock [59]. Maintenance of oxygen delivery is essential to prevent hypoxia, inflammation, and organ dysfunction [60]. Secondly, HSL could reverse shock induced acidosis. Third, evidence suggests that lactate has beneficial metabolic effects including improved cardiac efficiency. While Kline et al found that HSL increased cardiac work and cardiac efficiency after haemorrhagic shock, in 2000 Barbee et al.[6] found that depletion of endogenous lactate reduced the cardiac efficiency in a similar model of isolated rat hearts after haemorrhagic shock. Studies in human patients with congestive heart failure found that increased myocardial lactate consumption was associated with lower myocardial oxygen consumption and increased stroke volume[14]. Hence, HSL infusion has several beneficial properties if administered during uncontrolled bleeding and haemorrhagic shock. However, the therapeutic priority must be to stop the bleeding to prevent lethal blood loss.

Lactate as a Cardioprotective Treatment (n=3 studies)

Study results: A 2021 drug discovery study in a zebrafish model of AHF conducted by Haege et al. [32] identified lactate as a cardiac protectant. They found that lactate inhibited inflammation and cardiac hypertrophy. AHF was induced by aristolochid acid which led to human-like disease with cardiac hypertrophy, severed cardiac fibers, loss of endocardium, and gradual weajening and subsequent cessation of cardiac contractility. The study was designed to identify natural products that was beneficial to AHF, hence the authors tested nearly seventy herbal crude extracts. They identified the compound A2-4-2-4 which inhibited inflammation and cardiac hypertrophy by reducing MAPK signaling activity as well as COX-2 gene expression. MAPK cascades are known to modulate hypertrophic responses to pressure overload [61,62] as well as promotion of inflammatory cytokines. COX-2 is known to play a key role in development of cardiovascular disease [63]. Following chemical analyses found that A2-4-2-4 was almost pure lactate. Subsequently, the authors tested pure sodium lactate and found at-

tenuation of AHF and inflammation as well as cardiac hypertrophy. The authors concluded that lactate could serve as a cardiac protectant and a new therapeutic agent for AHF.

In 1959 Bellet el al. [64] investigated the effects of 1 molar sodium lactate infusion in dogs during quinidine intoxication. Dogs were sorted to one of two groups: a control group receiving nothing but continuous quinidine infusion until death (n=7) or a group receiving quinidine in the same manner and treated with one molar HSL during various stages of quinidine intoxication (n=12). Cardiotoxic effects of quinidine, which manifested as hypotension and ECG alterations. These effects were reversed in the HSL group during early stages of intoxication with increased blood pressure and reduction of ECG changes. The group described several possible mechanisms. First, infusion of a hypertonic fluid leads to expansion of extracellular space and thereby the concentration of quinidine was reduced. Second, infusion of HSL leads to alkalosis which shifts potassium ions from extracellular space into the cells reducing cardiotoxic hyperkaliemia. Also, the group found an increase in blood pressure which could be the cause of increase in CO and coronary flow, the expansion of plasma and blood volume or a combination of these. Finally, the group argued that lactate *per se* may act as myocardial substrate in Krebs cycle as a readily oxidizable fuel. In more advanced stages of quinidine intoxication, the group found that HSL was not able to reverse the cardiotoxic effects.

Later in 1959 the same group used a similar set up to examine effects of HSL on cardiotoxic effects of procaine amide intoxication [65]. The group found that HSL was able to diminish the cardiotoxicity of procaine amide even during later stages of intoxication. Again, the group described several possible mechanisms. First, a decrease of procaine amide in the same way as observed in the quinidine study. Second, improvement of intoxication induced acidosis and hyperkaliemia as HSL leads to alkalosis. Finally, a direct metabolic effect of lactate.

Discussion: Lactate as a Cardioprotective Drug

In a drug discovery study conducted by Haege et al [32]., lactate was identified as a potential cardioprotective agent for AHF. The researchers discovered that lactate administration resulted in the downregulation of MAPK activity and COX-2 gene expression. As a result, they observed reduced cardiac hypertrophy and inflammation. In a separate study conducted by Besnier et al [22]., the infusion of HSL was found to decrease the levels of pro-inflammatory cytokines, including TNF-α. The findings from Haege et al. provide a possible explanation for the decreased cytokine levels observed by Besnier et al., as increased MAPK pathway activity is known to elevate the levels of pro-inflammatory cytokines, such as TNF-α [66]. TNF-α exert as a pathogenic factor in cardiac fibrosis and heart failure associated with a large decrease in survival [67] and can upregulate COX-2 further increasing levels of inflammatory cytokines [68,69]. During their study of HSL infusion during MI, Zhang et al [30]. found that HSL led to less myocardial fibrosis and enhanced expression of STAT-3. STAT-3 is known to play multiple protective roles in the heart and downregulate production of pro-inflammatory TNF-α production by monocytes [70,71]. Hence, the findings by Zhang et al. could provide another explanation the findings of Besnier et al. Together the findings by the studies included in this review indicate that lactate could serve as a cardioprotective drug in multiple situations as MI or AHF by regulation of multiple cardioprotective and anti-inflammatory pathways.

The early studies by Bellet et al. suggests that HSL *per se* have beneficial metabolic effects. This agrees with findings already discussed in earlier sections in this review [6,14,31]. The healthy heart favors Free Fatty Acids (FFA) for ATP generation while the failing heart have higher dependency on lactate and ketone oxidation [72]. Though, the ATP yield per molecule is greater for FFA's than for lactate the ATP yield per consumed oxygen molecule is greater for lactate than FFA [12,73]. A 2014 clinical study found that HSL infusion increased CO in patients with acute heart failure [12]. Together these findings indicate that lactate could prove a vital energy substrate in a situation of a starving myocardium e.g., heart failure.

Concluding Remarks

The number of studies investigating the haemodynamic and cardiovascular effects of exogenous lactate continues to grow. However, the number of conducted studies remains limited, and their quality varies, particularly in terms of reporting randomization and blinding. Also, some of the results are somewhat conflicting. The study designs of the included studies exhibited flaws, and their reporting on randomization and blinding was inconsistent. Out of the twelve studies included, eight reported implementing randomizations, while three studies did not provide information on randomization, and one study was not randomized. Only one out of twelve studies fully employed blinding in their design, while seven studies did not report whether blinding was incorporated, and one study had partial blinding. The remaining two studies did not implement blinding (Table 1).

Nevertheless, most evidence suggests that exogenous HSL could be an alternative treatment method in a variety of situations and disease states. Lactate has beneficial effects in myocardial crisis situations such as shock situations, cardiac arrest, and myocardial infarction. Henceforth, the field of metabolic approaches to these situations remains highly relevant. Future studies should prioritize the development of high-quality randomized blinded translational studies with strong clinical translatability and comprehensive reporting. This approach will enhance the quality of data, translational value, and reproducibility.

study design and reporting to ensure more reliable results.

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