Critical Care

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Cardiovascular effects of lactate in healthy adults: D-lactate, the forgotten enantiomer—authors' reply

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To the Editor,

We thank Drs. Stevic, Argaud, and Cour for their interest in our recent article entitled *Cardiovascular Effects of Lactate in Healthy Adults* [1]. Indeed, utilizing a racemic hypertonic sodium lactate (HSL) solution, the composition of the enantiomers L- and D-lactate is balanced, and we agree that recognition of chirality is essential to further comprehend our results. However, additional important aspects must be considered to fully explain the potential hemodynamic benefits of HSL treatment.

The commentary by Stevic et al. [2] raises concerns regarding potential toxicity from D-lactate accumulation, particularly in critically ill patients. While it is true that D-lactate is metabolized less efficiently than L-lactate [3], the clinical relevance of this remains unclear. In healthy individuals, D-lactate is present at negligible concentrations and is readily excreted in the urine [4]. In our study, we only measured circulating L-lactate, and thus, we can only speculate on the levels of D-lactate [1]. Interestingly, a prior study of healthy participants utilizing a similar infusion regimen to ours demonstrated comparable circulating levels of L-lactate (2.8–4.0 mmol/L), with slightly lower levels of D-lactate (1.7–3.0 mmol/L) [4]. This difference was attributed to lower endogenous D-lactate production. Importantly, metabolic clearance of D-lactate appeared to be efficient, despite preferential utilization of L-lactate. While L-lactate is typically converted to pyruvate via L-lactate dehydrogenase (L-LDH), D-lactate may also be converted to pyruvate through D-LDH, an enzyme enriched in the liver and kidneys [5]. These findings suggest that D-lactate, although less abundant in the bloodstream, may still undergo metabolic processes.

Despite concerns regarding potential D-lactate toxicity, no studies to date have demonstrated clinically relevant adverse effects following exogenous administration in humans at doses comparable to those used in our study. Notably, endogenous accumulation of both L- and D-lactate can contribute to lactic acidosis [6]. While L-lactic acidosis is commonly observed in clinical settings, D-lactic acidosis is rare and often associated with short-bowel syndrome, where excessive D-lactate is produced and absorbed from the gastrointestinal tract [7]. Furthermore, although D-lactate accumulation has been linked to neurological symptoms in patients with mutations affecting D-LDH function, these conditions

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are often accompanied by the accumulation of multiple organic acids, complicating the interpretation of D-lactate toxicity [8]. Importantly, no side effects resembling "D-lactate encephalopathy" have been reported in healthy individuals receiving D/L-lactate infusions, even at blood D-lactate concentrations reaching 5 mmol/L [3, 4]. Nonetheless, further investigation is warranted, particularly in critically ill patients.

Recent studies from our laboratory provide further insights into the potential therapeutic effects of racemic HSL infusion [9]. In a porcine model of cardiogenic shock, HSL administration improved hemodynamics, including increased cardiac output and peripheral perfusion, alongside enhanced mitochondrial function [10]. Similarly, in a porcine cardiac arrest model, the same racemic HSL solution (Monico, S.P.A, Italy) demonstrated hemodynamic benefits and reductions in biomarkers of cardiac and cerebral injury [11]. These findings strengthen the hypothesis that HSL, even as a racemic mixture, exerts beneficial cardiovascular effects in critical conditions. While Stevic et al. correctly highlight the potential metabolic benefits of L-lactate treatment, it is important to note that many of their cited studies do not exclusively utilize L-lactate. In fact, few studies have explicitly tested this hypothesis using pure L-lactate, and it is often unclear whether the lactate infusion used was racemic (D/L-lactate) or contained only the L-enantiomer [12]. Moreover, existing concerns regarding potential D-lactate toxicity are primarily based on high-dose administration in small-animal models or retrospective data with multiple confounding factors [13, 14]. While further research is warranted, particularly in critically ill populations, current evidence does not indicate clinically relevant D-lactate toxicity following racemic HSL infusion in healthy individuals or in large-animal models.

Our study observed an alkalizing effect rather than acidosis following HSL administration, which the commentary [2] attributes to L-lactate metabolism counteracting any potential acidifying effect of D-lactate. However, an often-overlooked factor is that we administered sodium lactate, which, as a conjugated base, directly contributes to alkalization. Furthermore, according to the Stewart model of acid–base balance, the increase in strong ion difference following sodium lactate administration leads to alkalemia. This mechanism, independent of lactate metabolism, likely explains the observed alkalizing effect, regardless of enantiomer composition.

The commentary by Stevic et al. also raises an important question regarding whether HSL-induced improvements in left ventricular function stem from direct effects on cardiomyocytes or indirect systemic mechanisms. While our study was not designed to isolate these effects, recent animal studies provide valuable insights. High-dose racemic HSL administration has been shown to increase cardiac output and reduce systemic vascular resistance in healthy pigs [9]. However, left ventricular contractility was not significantly affected. In a cardiogenic shock model, lower-dose infusion with the same HSL solution similarly reduced systemic vascular resistance while also improving cardiac contractility, suggesting a direct inotropic effect [10]. In fact, a direct metabolic effect was also noted, as myocardial mitochondrial function improved. Thus, individual cardiovascular effects of lactate treatment may be both dose- and pathophysiology-dependent. Although a prior study did not observe direct effects of lactate on the isolated heart, this may have been influenced by the abrupt buffer shift inherent to such experimental setups [13]. Notably, recent findings indicate that lactate treatment enhances left ventricular developed pressure in the isolated heart and induces vasorelaxation in isolated arteries in a dose-dependent manner [15], corroborating observations from large-animal studies and our human cohort. This growing body of evidence supports the hypothesis that HSL exerts beneficial cardiovascular effects not only via systemic hemodynamic changes but also through direct myocardial actions.

In conclusion, while current evidence does not support harm from racemic HSL treatment in humans, we share the recognition by Stevic et al. that further investigation is warranted before considering its use in critically ill patients.

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Declarations

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Not applicable.

Consent for publication
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Competing interests
The authors declare no competing interests.

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