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Short Report

Local but not Systemic Capillary Lactate is a Reperfusion Biomarker in Experimental Acute Limb Ischaemia☆

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ABSTRACT

Introduction: Systemic capillary lactate, an end product of cellular anaerobic metabolism, has not established credibility in monitoring limb reperfusion. We assessed, in mice, whether local capillary lactate, arising from the reperfused limb, might be a relevant biomarker of reperfusion.
Report: Systemic and local capillary lactate were sampled in the non-ischaemic and in the ischaemic limb. Only local lactate concentrations significantly increased after 2 h of ischaemia and decreased after reperfusion.
Discussion: Local, but not systemic, capillary lactate appeared as a potential reperfusion biomarker in this experimental acute limb ischaemia model.

Acute limb ischaemia is a common and critical vascular disease with a mortality rate of 15–20%. Post-revascularisation care requires careful limb vascular monitoring for early critical ischaemia recurrence. However, in emergencies, such clinical follow-up might be difficult. Peripheral pulse status is not strongly correlated with tissue perfusion and to clearly determine whether the revascularisation is successful remains a challenge.

Lactate, the end product of cellular anaerobic energetic metabolism, which is a key biomarker of tissue hypoxia, is of interest as an ischaemia biomarker. Systemic lactate has not convincingly been useful in monitoring limb reperfusion.[1] However, microdialysis demonstrated a short time course of lactate normalisation in muscular tissue after revascularisation.[2]

We tested the hypothesis that local capillary lactate arising from the ischaemic limb might be a better biomarker for early reperfusion than systemic lactate, and determined simultaneously systemic and local lactate kinetics in a one-limb ischaemia–reperfusion (IR) mouse model. Skeletal muscle mitochondrial function, impaired following IR, was also analysed.[3,4]

Report

Experimental design, blood and muscle sampling and analysis

Mice were separated into two groups: the sham group (SHAM, $n = 13$), which did not undergo, IR, and the ischaemic group (IR, $n = 12$), which had left limb ischaemia induced by a tourniquet applied for 2 h followed by a 2-h reperfusion. Then, gastrocnemius muscles were excised for mitochondrial respiration analysis. The left leg was considered as ischaemic (IR-ISCH) and the right contralateral leg was considered as non-ischaemic (IR-CTL).[3]

Local and systemic capillary lactates were measured simultaneously before ischaemia, 2 h after ischaemia (I) and 2 h after IR, using the Lactate Pro© device (LT170, Arkray, KGK, Japan).[5]

Mitochondrial maximal oxidative capacities were investigated using glutamate–malate in saponin-skinned gastrocnemius fibres.[3]

The investigation was carried out in accordance with Helsinki Accords for Humane treatment of Animals during Experimentation (institutional approval no. AL/02/21/12/09).

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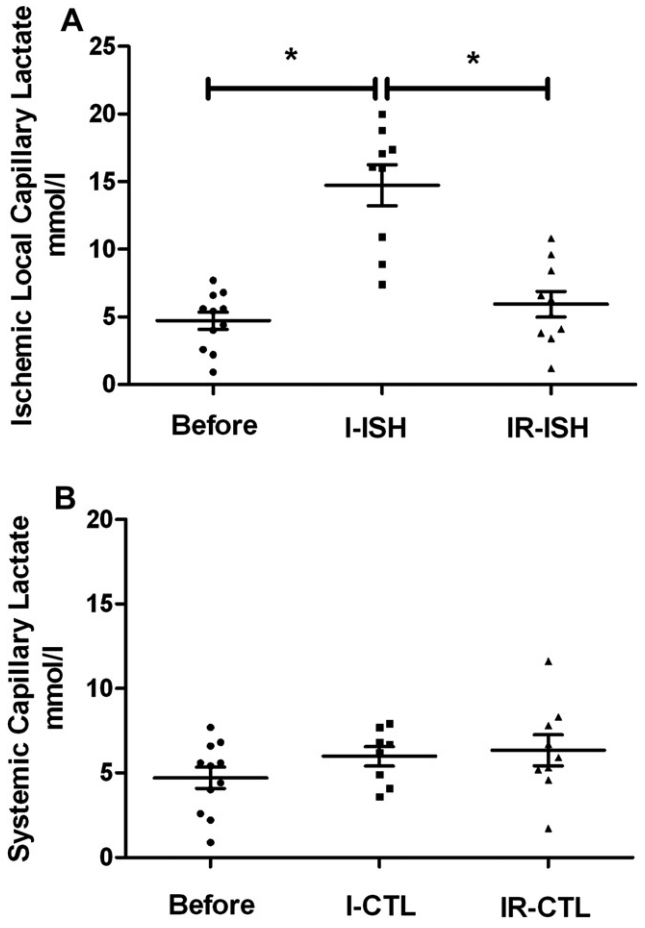

Figure 1. Capillary lactate values (A): local capillary lactate sampled at the ischaemic leg level (B): systemic capillary lactate sampled at the contralateral non-ischaemic leg level Data are presented in three experimental conditions: before ischaemia, after ischaemia and after ischaemia–reperfusion in the ischaemic leg (IR-ISCH) and in the non-ischaemic leg (IR-CTL). Horizontal line at the mean and vertical bar for the SEM. ($n = 11$) $^{*}p < 0.05$ (before vs. I-ISCH: $p = 0.00013$, I-ISCH vs. IR-ISH: $p = 0.00017$).

Statistical analysis

Data were expressed as mean ± standard error of mean (SEM). A one-way analysis of variance (ANOVA) was used, with the Newman–Keuls post-test analysis and *t*-test for requiring analysis. $p < 0.05$ was accepted as significant.

Results

Mitochondrial respiratory chain oxidative capacity (V_{max}) was similar in sham animals and in the non-ischaemic contralateral leg of the IR animals (8.58 ± 0.85 vs.9.39 ± 1.33 μmol min^{-1} g^{-1} dry weight, $p = 0.59$, in SHAM and IR-CTL, respectively).

V_{max} was significantly decreased in ischaemic muscle as compared with SHAM and IR-CTL (5.40 ± 0.95 vs. 8.58 ± 0.85 and 9.39 ± 1.33 μmol min^{-1} g^{-1} dry weight, $p = 0.04$, −30% ± 14% and $p = 0.03$, −32% ± 12%, respectively).

Ischaemia significantly increased local capillary lactate levels in the ischaemic leg, compared to baseline value (14.73 ± 1.50 vs.4.71 ± 0.64 mmol l^{-1}, in I-ISCH, $p = 0.00013$, Fig. 1).

The small increase in lactate value in the systemic leg failed to reach statistical significance (5.99 ± 0.57 mmol l^{-1} in I-CTL, $p = 0.62$).

Thus, lactate increase was significantly greater in the ischaemic than in the non-ischaemic leg (+419% ± 173, vs. +108% ± 93, for I-ISCH and I-CTL; $p = 0.031$).

After 2 h of reperfusion, local capillary lactate levels significantly decreased (5.94 ± 0.95 mmol l^{-1}, $p = 0.00017$). Systemic lactate value failed to change significantly (6.34 ± 0.91 mmol l^{-1}).

Thus, lactate variation was significantly greater in the ischaemic than in the non-ischaemic leg (−59% ± 8, vs. +13% ± 22, for IR-ISCH and IR-CTL respectively, $p = 0.015$).

Discussion

In accordance with data reported after IR in rodents, we observed a decreased muscle mitochondrial maximal oxidative capacity after this 2-h ischaemia–2-h reperfusion protocol in mice. Such results further support that mitochondria are early target of IR injury.[3]

Although systemic lactate is of prognostic interest, its slow and progressive changes preclude use in the early diagnosis of re-thrombosis.[1]

Local capillary lactate, sampled directly at the ischaemic leg level, demonstrated both a rapid increase during ischaemia and a rapid decrease during reperfusion. Such kinetics are in agreement with data obtained using microdialysis, and could allow an early diagnosis of successful reperfusion.[2]

In summary, this study demonstrates that local, but not systemic, capillary lactate levels might be reperfusion biomarkers after limb IR. Since capillary blood lactate monitoring is a rapid and repeatable bedside method,[5] clinical studies are warranted to test whether local lactate kinetics might be helpful in determining the success of revascularisation in vascular surgery in man.

Conflict of Interest/Funding

None.

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