



June 19, 2013

Dear Dr. Wang,

Please find enclosed the edited manuscript in Word format (file name: WJCCM ms 3575 Gurji et al R1.doc).

Title: Pyruvate-fortified resuscitation stabilizes cardiac electrical activity and energy metabolism during hypovolemia

Authors: Hunaid A. Gurji, Daniel W. White, Besim Hoxha, Jie Sun, Albert H. Olivencia-Yurvati, Robert T. Mallet

Name of Journal: *World Journal of Critical Care Medicine*

ESPS Manuscript NO: 3575

The manuscript has been improved according to the suggestions of reviewers:

We thank the reviewer for evaluating our manuscript, and are sincerely grateful for the favorable comments regarding the quality of the manuscript and the potential impact of the work.

1. The reviewer commented: "My only question/comment - if the data is available (I think it might further support the clinical potential of their findings - but not critical to the overall value of this manuscript) - do the authors have any pre/post hemodynamic data. While in the animal model it appeared that the starting blood pressures and heart rates were the same - and the initial response to controlled bleeding was intended to be the same - to further support their findings - is there physiologic (i.e. blood pressure and/or heart rate) data to suggest a substrate enhanced fluid had an additional benefit. In other words - did the blood pressure go up more in the enhanced group than the LR group. If this data is available and can easily be incorporated and discussed without adding further significant length to the manuscript, I think it would add to the potential translational benefits of their findings."

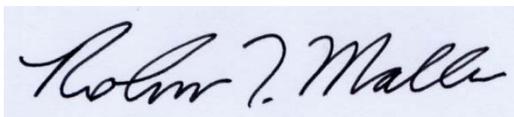
Response: Arterial blood pressure was monitored and recorded during the experiments. In accordance with the reviewer's recommendation, we now report mean arterial pressure values (new Figure 1 of revised manuscript; new figure legend lines 561-567) at the same time points as the QTc values (formerly Figure 1, now Figure 2). A new paragraph (lines 192-200) has been added at the beginning of the Results section summarizing these results, which are briefly discussed (lines 276-278). The new figure documents the reductions in mean arterial pressure produced by the exsanguination, the effectiveness of fluid resuscitation at restoring blood pressure, and the subsequent decline in blood pressure 3.5 h after completing resuscitation. Moreover, pyruvate-enriched Ringer's (PR) produced a greater increase in arterial pressure ($p < 0.05$) than did lactated Ringer's (LR), in accordance with previous reports of pyruvate enhancement of cardiac function [*cf. Mallet et al., Exp Biol Med* 2005;**230**:435-443 and references cited therein]. These treatment effects persisted but were no longer statistically significant ($p = 0.084$) at the end of the experiment. We note the decline in arterial pressure in the non-hemorrhaged time control group over the 6 hour protocol. Although the mechanisms of

this decline are undefined, it is likely due in part to the cardiodepressive effects of prolonged isoflurane anesthesia [Raner *et al.*, *Acta Anaesthesiol Scand* 1994;**38**:136-143; Graham *et al.*, *Can J Anaesth* 1996;**43**:495-502; Kehl *et al.*, *J Cardiothorac Vasc Anesth* 2003;**17**:709-714]. Although treatment effects on mean arterial pressure were detected, the manuscript remains primarily focused on the robust, persistent electrocardiographic effects of PR vs. LR resuscitation and the possibility that oxidative impairment of the creatine kinase energy shuttle, which was prevented by PR, may have contributed to the QTc instability in the LR group.

Significant textual revisions are indicated in red font in the revised manuscript.

Thank you again for publishing our manuscript in the *World Journal of Critical Care Medicine*.

Most sincerely yours,

A handwritten signature in black ink on a light blue background. The signature reads "Robert T. Mallet" in a cursive script.

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