I thank you for the careful review of my article. I take into account the Science Editor and the Reviewer comments, and I am pleased to submit the revised version.

Name of journal: ***World Journal of Cardiology***

ESPS Manuscript NO: 19963

Answers to the Reviewer:

Up-to-date publications: I can hardly find more recent studies on this subject. There are hundreds of publications on cardioplegia but few of them are on re-dosing interval. I added one reference on 60 minutes re-dosing interval for coronary artery bypass graft but this reference is from 1999. I would greatly appreciate suggestions of more recent works.

Solutions: We did not intend to compare different compositions of cardioplegia solutions. However, St Thomas solution being the arresting agent used in our protocol of intermittent warm blood cardioplegia, I added this information in the main text. Superiority of hyperpolarizing to depolarizing cardioplegia is suggested in experimental studies but I don't find any relevant studies in humans on re-dosing interval with hyperpolarizing agents. Furthermore, the ideal concentration of its constituents remains to be found.

Specific comment 1: I agree with the reviewer, continuous cardioplegia does not always provide optimal protection and is not always feasible, this is pointed out later in the review. However, from a theoretical point of view, continuous warm blood cardioplegia decreases oxygen consumption without inducing ischemia and this benefit must be pointed out.

Specific comment 2: References to one-shot cardioplegia for minimally invasive valvular surgery were made later in the review. However, I also added two more references. The role of temperature is outside the scope of this review. We do not intend to discuss composition of cardioplegia, injection site(s), or temperature but to focus on re-dosing interval. Details on composition, injection site or temperature may be mentioned in some studies when re-dosing is the major aim.

Specific comment 3: I agree with the reviewer on the fact that the technique is "in between" continuous and intermittent cardioplegia. As stated before in the text, this study is on discontinuous warm blood cardioplegia with interruption(s) of 5 to 15 minutes, and the authors postulate that short period of normothermic ischemia should be well tolerated if followed by adequate cardioplegic reinfusion. Therefore the longest ischemic time is the longest time off cardioplegia.

Specific comment 4: The text has been reworded accordingly to increase clarity.

Specific comment 5: The arresting agent was St Thomas and I added this detail in the text. For blood cardioplegia the concentration of potassium depends on both the variable concentration of potassium in the blood coming from the bypass circuit and the

constant concentration in the arresting agent (in St Thomas 800 mEq/L). Therefore the final concentration is not a constant, unlike in crystalloid cardioplegia.

Specific comment 6: I agree with the reviewer on the fact that ATP levels were lower in the group with intermittent warm blood microplegia than in the group with cold blood crystalloid cardioplegia. However, the difference was not significant and there were more patients with heart failure prior to surgery in the warm group. Of notice, average values during cardioplegia are within normal normoxic range of ATP concentrations (3-5 $mmol.kg^{-1}$). Furthermore, the dosages were done after 14 minutes of ischemia in the warm group versus 29 minutes in the cold group. The message of this work is to show that warm ischemia is harmless.
The reviewer stated: "it is highly unlikely that ATP levels increase during ischemia" and I agree on the fact that it is surprising. However, some decades ago, the medical community predicted that warm myocardial ischemia would induce irreversible damage to the heart and we now have an experience of more than 30 000 cases demonstrating the good tolerance of intermittent warm blood microplegia.

Specific comment 7: Newer references can be found further in the text: references 66, 35, 36, 37, 72 respectively from 2001, 2008, 2011, 2012 and 2014.

Specific comment 8: Yes indeed, high dose HTK solution means high volume. There is no agreement on the optimal volume or dose of HTK solution and some authors use 50 ml/kg while others use 20-25 ml/kg.