Author's response to reviews

Title: Genetic deletion in uncoupling protein 3 augments 18F-fluorodeoxyglucose cardiac uptake in the ischemic heart

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Response to Reviewer 1 report:

We would like to thank this reviewer for the constructive criticisms. We fulfilled all the issues raised by the reviewer and the manuscript has been modified accordingly.

1. Major comments

1.1 Pathophysiological aspects:

We provided some mechanistic explanation on the role of UCP3 protein in cardiac protection from ischemic injury (See Discussion, page 9, lines 172-175 and page 10, lines 176-180).

1.2 Methodological issue:

a. The definition of tracer uptake index has been better defined. As suggested, we also provided a separate analysis of FDG uptake in infarcted and remote areas (See Methods, page 6, lines 88-89 and Table 3). As discussed, this additional analysis supports the hypothesis that a metabolic shift in remote myocardium is a possible explanation of our data (See Discussion, page 9, lines 172-175 and page 10, lines 176-180).

b. The additional analysis performed (Table 3) also indicates that average SUV was similar in infarcted regions of UCP3 knockout and WT mice, but was almost double in remote areas of UCP3 knockout compared to WT.

1.3 Technical aspects:

We mentioned in a new paragraph that this study has some limitations (See Discussion, page 11, lines 203-208). First, serum glucose levels were not available at time of imaging. In addition, no dynamic acquisition was performed and cardiac glucose metabolism was indexed by SUV. This approach might have been hampered by the systemic effect of UCP3 deletion on glycolytic flux in the whole body tissues. However, the requested analysis of FDG uptake in non-cardiac tissue indicates that SUV was independent from UCP deletion and myocardial infarction (See Table 4). These data suggest that blood tracer availability for myocardial uptake was not altered in UCP3-/- mice.

1. Minor comment (typo)
At line 188, the sentence: “Moreover, and UCP3-/- mice displayed a significant worsening in cardiac function after coronary artery ligation compared with WT” has been corrected.