Digital ventilated cage (DVC®) in Covid19 Research: immediate mice sickness detection

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Introduction

Since the Pandemic start, a global effort raised to identify the mechanisms of action of the SARS-CoV-2 (Covid19) virus and find a cure. In preclinical research, several animal models have been proposed ranging from Syrian Hamsters up to Non-Human Primates. Unfortunately, the most used animal model, namely the mouse, does not properly show signs of infections because of lacking the receptor by which the virus can enter the murine cells. In February 2020, Jackson Lab thawed the **K18-hACE2 mice**, initially created for studying the SARS Virus (McCray et al., 2007), that are carrying the human ACE2 receptor, which is "lock" by which the virus enters the cell with its "key" the spike protein. This mouse model has been presented in several articles as one of the most wanted by several journals (scientific or more for the general audience, two are mentioned below).

https://www.nytimes.com/2020/03/14/science/animals-coronavirus-vaccine.html

https://www.nature.com/articles/d41586-020-00698-x

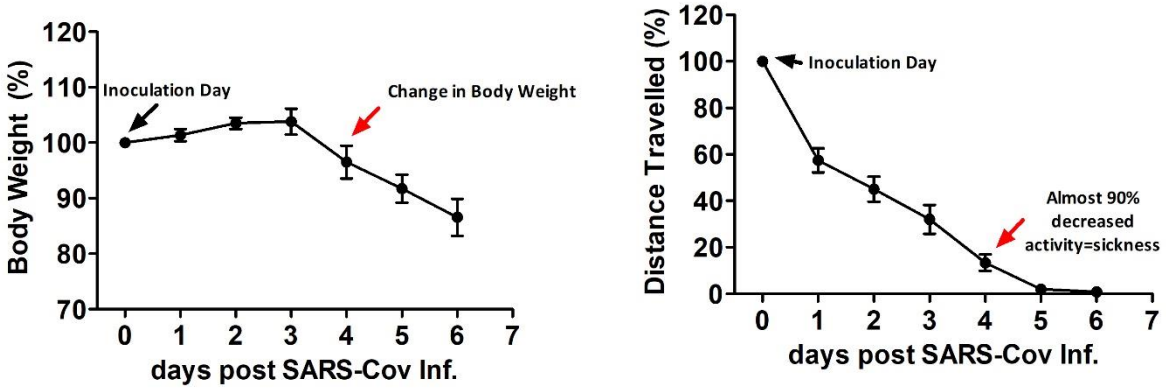
As the mice have become only available in early summer 2020, the most prominent centres in the world have started to work with those mice to evaluate the viral response and its cures (drugs or vaccines). Most of publications about infectious disease, including *in-vivo* laboratory animals' experiments, use body weight as output for animal welfare. Two recent publications indicate that body weight loss, as indicator for clinical sign, is visible only from day 4 onwards (Jiang et al., 2020; Winkler et al., 2020). However, we tested the hypothesis of whether the locomotion as measured of clinical sign can anticipate the reported body weight loss.

Methods

In collaboration with RI-MUHC BSL3 Facility at McGill University, Montreal, we evaluated through our non-intrusive and outside of the cage technology directly in the home rack called Digital Ventilated Cage (DVC®) (Voikar and Gaburro, 2020) the clinical signs of those mice upon SARS-CoV2. To this end, Eight K18-hACE2 (C57Bl/6J background) mice were exposed to the SARS-COV-2 virus, and the locomotion was assessed for six days. Body weight was taken daily as reference. We

compared the occurrence of disease progression against the gold standard for animal welfare in infectious disease namely daily body weight check.

Results & Brief Discussion



The left graph shows that infected K18-hACE2 mice display a first change in body weight (expressed as %) only at day 4 after SARS-CoV-2 infection. The trend of body weight loss continues, up to 10%, until day 6. Instead, looking at the right graph in which the distance travelled (%) is plotted, it is notable that at Day2 post infection, there is a reduction of 50% of the distance travelled. As the infection progresses, there is a depression of the activity to 90%. Additionally, after five days, the animals are completely immobile. These results indicate sickness of the animal, and it is the first data of its kind, showing that SARS-CoV-2 impacts in such a significant way the animal locomotion. These body weight findings are also in line to what was recently published (Jiang et al., 2020; Winkler et al., 2020) in which only a relative decline in body weight was observed.

Importantly, the locomotion results are in line with what was reported before by other studies, namely that after seven days of SARS inoculation, the hACE2 mouse model become very sick up and eventually died after seven days (McCray et al., 2007).

Conclusion

The home cage monitoring system demonstrated its potential to identify the viral effect which can not be objectively immediately with gold standard measures such body weight. Current research is underway to understand what the effects are via different vaccines. Additionally, because the technology can be applied in BSL-3 and 4 environments, the same system could also be used for

automated, high-throughput, and unbiased data collection to support neurological diseases such as rabies or other zoonotic models.

Taken together, these results show that body weight only as “animal welfare” biomarker for infection progression might not be sufficient and viable locomotion data should be taken into consideration for disease progression assessment.

Acknowledgments

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