Space Cardiovascular Pharmacology
Consolider nos fondamentaux
Créer un avantage compétitif via les offres et les services
Engager les collaborateurs

Context
Spaceflights, Microgravity and early cardiovascular aging
Space pharmacology challenges
PK/PD studies in space
Pharmacological countermeasures
Microgravity
Cardiovascular deconditioning

Long term (> 6 months)

Muscular atrophy +++

«chicken leg»

Metabolic syndrome

↓↓↓↓ Physical activity

Stress: prolonged lockdown
Vibration / Acceleration
+++ Cosmic radiations

Cardiac and arterial remodeling as Early vascular ageing (EVA)

Forced Sedentary lifestyle

What is Early Vascular Ageing?

https://www.youtube.com/watch?v=7s0_Rkg_bRE
Animation by VasAgeNet
Arterial stiffness (pulse wave velocity or distensibility) are undisputed hallmarks of vascular aging.

Effect of long-term spatial conditions on carotid distensibility

In parallel with insulin resistance

Boutouyrie et al, submitted

“Cocktail” head down tilt

0 20 40 60 80
Vascular age (years)
# Microgravity
Pharmacology in space

## Why is it needed?
- Profound modification of body in space
  - Composition and metabolism affecting drug pharmacokinetics and pharmacodynamics
- No pharmacological countermeasures yet proposed for space related health issues including early vascular ageing
- “Older astronauts” to be expected with potential health issues
- Long term flights $\rightarrow$ increased risk of disease to be managed

## Why is it missing?
- Obstacles for Pharmacological studies
  - Logistical and technical constraints of sample biologics fluid
  - Difficulties of dosages
  - Analysis on board not feasible yet
STRAATEGY

- Development of new methodologies based on LCMS/MS for drug detection/dosage
- Define a strategy for pharmacological countermeasures
Quantitative LC-MS/MS dosage of 24+ cardiovascular drugs, urine samples, adherence to antihypertensive medication, routine clinical practice at our laboratory

Adaptation to Space requirements

Hamdidouche et al. J. Hypertens, 2017
Kably et al, Curr Op Hyper, 2020
Innovative dried matrix spot technique use (DUS, DBS)* applied to drug dosage, coupled with LC-MS/MS dosage could be the ideal methods for Space Pharmacology.

My Master’s research: Validation of 5 cardiovascular drugs detections on Dried Urine spot (paper in progress)

PhD to be started…

* DUS = Dried Urine Spot; DBS = Dried Blood Spot
# Dried Matrix Spot

## Characteristics

### Advantages
- Easy and fast collection
- Not limited to drugs (infectious disease etc)
- Self-collection by non-professional health care
- Safe, lower risk of biohazard
- Minimal requirements for transport (< 3 grams/sample)
- Resistance to stress and conditions of storage
- Very small volume of biological fluids needed
- Apt to repeated biological fluid sampling
- Very low cost
- Applicable to extreme environments and remote areas

## Limits
- Not all drugs are detectable (according to their chemical properties)
- Long development for each compound to detect
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Renouer avec la croissance
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*VICA : volatile incertain Complexe Ambigu

Pharmacology studies
Research Platforms for Pharmacology studies

Self management of samples in isolation

Cardiovascular Monitoring and Pharmacology on Mars COSMOS
- Isolation / confinement
- Hostile environment

Mars Desert Research Station (MDRS)

Dec 2021

Microfluidics in microgravity

Pharmacology Space Kit PSK
- Microgravity (lunar/martian gravity)
- Hypergravity

Parabolic flight

Mars 2022

Changes in drug metabolism induced by microgravity

Pharmacology Space Kit PSK
- Weightlessness simulation
- Inactivity/unloading

Bed Rest

2022
2 weeks Simulation in December 2021

The Trans-Atlantic Mars Society MDRS Team will conduct our project:

- **Crew Commander**: James Burk
- **Executive Officer and Safety Officer**: Aline Decadi
- **Crew Engineer**: Julien Villa-Massone

- **Crew Scientist**: Frederick Bigrat
- **GreenHab Officer**: Cécile Renaud
- **Crew Geologist**: Guillaume Thirion
At MDRS

• COSMOS - PASKAL-Caffeine
  • A screening study of caffeine and metabolites in blood and urine

Why caffeine?
A screening study of caffeine and metabolites in blood and urine

**Why caffeine?**
- Caffeine is a natural psychoactive substance naturally present in coffee → avoids regulatory issues
- To date, no terrestrial simulation model has yet been validated for the PK/PD study under space conditions (Kast J et al, 2017; Blue RS et al 2019)
- Cytochromes (CYPs) are critical enzymes for drugs metabolism
- CYP1A2 is a well-known metabolic pathway involved in elimination of common drugs (Lidocaine, Melatonine, Caffeine…) included in ISS medical KIT (Wotring VE 2015)

**Objectives**
- To evaluate the feasibility of blood/urine collection for DBS, DUS
- Propose a unique PK exploration using coffee as a probe
- To have a functional picture of a main metabolic pathways and their modifications during the study
COSMOS - PSK-Caffeine
A screening study of caffeine and metabolites in blood and urine

Subjects: MDRS (Utah) team as a whole
Training: The finger-prick test will be supervised by our team during the 1 day training at INSERM U970 (Paris, France)
A video instruction will also be accessible for a self-instructive material and a effective training for collection of DBS/DUS

Restrospective LC-MS/MS analysis at our pharmacology lab
- 4 replicates on 1 card
- Storage conditions RT
The D-day, standardized caffeine intake (one cup of coffee, mug of tea, no caffeine after)
COSMOS - MAEVA
MArs Early Vascular Ageing monitoring

Hypothesis
- Aortic PWV increases during space flight, and will remain high after Mars landing and does not normalize after return

Proposition
- A cardiovascular follow-up of the Mars analogue mission to all participants (PWV and blood pressure)

Material
- Assessed non-invasively by the pOpmètre®, connected weighing scale Withings®
- Advantages are simplicity, rapidity, feasibility, acceptability by patients, suitable to transport

Objectives
- To evaluate our procedure and test our material in isolation
- To evaluate the impact of extreme environment and confinement on PWV/EVA and vascular modifications during a Mars Analogue Mission
- PWV may serve for blood pressure estimation

https://www.youtube.com/watch?v=4aFnQ_0_bOI
Why COSMOS and PSK projects are crucial for long-term Space missions?

Cardiovascular health is essential for astronauts for fulfilling missions and for their future life. Investment in manned Space missions require optimal drug safety for fully operational astronauts.

COSMOS and PSK will make possible:

- To test technologies and procedures of early vascular aging in extreme environment: pOpmetre® and the connected balance Withings® as health monitor
- To establish rigorous protocols for handling and storing human Martian biological samples before returning to “Earth” for analysis
- To test a unique smart support, multifunctional, easy to transport and economical: the dried matrix. Very simple “analogic and robust” methodologies not requiring IT resources. Final objective is to improve the comfort of Marsonauts/ Astronauts

MDRS/ Parabolic Flights / BED REST provide a unique research environment to validate new technologies and to define new control strategies
Thank you!

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